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UNOFFICIAL TRANSCRIPT*
WASHINGTON STATE PHARMACY AND THERAPEUTICS COMMITTEE MEETING
April 19, 2006
Marriott Hotel Seatac
9:00am – 4:00pm

Committee Attendance:
Angelo Ballasiotes, Pharm D
Robert Bray, MD
Carol Cordy, MD (Vice Chair)
Jason Iltz, Pharm D
Janet Kelly, Pharm D
Daniel Lessler, MD (Chair)
Patti Varley, ARNP
Kenneth Wiscomb, PA-C

Consultant: Sharon Farmer, MD

9:00 a.m. - Committee came to order.

Dan Lessler: Washington State P&T Committee Meeting. Today we have really two primary topic areas. The first is going to be a presentation on the update of antidepressants, and then we are going to be spending considerable time on the atypical antipsychotics. I did want to let people know that later we're going to be joined by Dr. Sharon Farmer. And I will introduce her when actually she joins us as a consultant related to the atypicals. I also wanted to just let people know that today is really going to be a day for hearing evidence, hearing stakeholder input and having discussion and that we're not actually expecting today on the atypical antipsychotics to have any recommendation- formal recommendation from the committee.

So with that, Jeff, are there any other announcements that you have? Or, Duane or other folks?

Male: That we have update slides for the atypical antipsychotics that we left on the table. That's hot off the press yesterday. So that will- they're out on the table.

Dan Lessler: All right. And so I think we can start in with the update on the second generation antidepressants and, Jeff, can you introduce our guest? He's on the phone.

Jeff: Our reviewer for this is Dr. Gerald Gartlehner who is from UNC, and I believe, Gerald, you're on the phone now?

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Gerald Gartlehner: I'm on the phone.

Jeff: Good. So we can go ahead and get started.

Dan Lessler: Do you want to- why don't you introduce yourselves at the front here, the members of the committee?

Jason Iltz: Jason Iltz, P&T committee member.

Bob Bray: Bob Bray, P&T committee member.

Dan Lessler: Dad Lessler, Chairman, P&T.

Carol Cordy: Carol Cordy, P & T committee member.

Patti Varley: Patti Varley, P&T committee member.

Janet Kelly: Janet Kelly, P&T committee member.

Jeff Graham: And Gerald, your slides are up now.

Gerald Gartlehner: Okay.

Jeff Graham: So, Gerald, we're looking at the very first slide, the title slide, so you can direct us from there.

Gerald Gartlehner: All right. Okay. Welcome, again. My name is Gerald Gartlehner. I'm from the RTI UNC evidence based practice and I will present the findings of the update of the systematic review on second generation antidepressants. And in general for this update no changes were made on any key questions or eligibility criteria. On slide two I'm just summarizing the drugs of interest again. Overall we have refused evidence on 11 second generation antidepressants; six SSRIs and five other second generation antidepressants. Slide three our populations of interest were adult outpatients with major depressive disorder, dysthymia, generalized anxiety disorder, obsessive compulsive disorder, panic disorder, post-traumatic stress disorder and premenstrual dysphoric disorder, as well as pediatric outpatients with major depressive disorder. On slide five overall for this update we included 22 new studies and they are broken down by study design on slide five. And I've just realized the data numbers do not add up and I apologize for that. It should read three studies of other designs. In the presentation I will focus primarily on the head-to-head trials since they provide the best evidence. And slide six summarizes the individual head-to-head comparisons. And as you can see this time, they were mainly studies comparing Citalopram and Paroxetine to other second generation antidepressants.

Slide seven, for major depressive disorder we found four new head-to-head trials; two of them were comparing Citalopram to Escitalopram and both of these studies show that Escitalopram was more efficacious than Citalopram for the treatment of MDD. The table on slide nine summarizes studies comparing Escitalopram to

Citalopram. And as you can see, overall we have four RCTs comparing Escitalopram to Citalopram; three are rated fair, one is rated good. The response rate at eight weeks consistently present a greater efficacy of Escitalopram, although the differences are not always statistically significant and the differences in response rates are rather substantial in some studies. For example, the [unclear] et al study recorded a 64% response rate for Escitalopram compared to a 53% response rate for Citalopram and Moore et al reported a 76% versus a 61% response rate. Also when reported remission rates usually favored Escitalopram over Citalopram. However, there are some caveats with these findings and it needs to be noted that both drugs are produced by the same manufacturer, which is [unclear]. Citalopram is available as a generic drug now while Escitalopram is still patented. So it is conceivable that publication by us might play a role, however at this point we do not have any evidence that would support publication by us.

So definitely the most interesting findings for this update. However, to put findings into better perspective, I would like to give you a preview of the upcoming updated report, which will be released in [unclear] in the end of May. And what we did for the new update is that we conducted meta-analysis on these studies. And slides 10 and 11 show two meta-analysis that are not included in the current report yet. So, on slide 10 we pulled the data from the study in table nine, achieved a summary effect and the meta-analysis on slide 10 is a relative risk meta-analysis of response rate on the Hamilton depression rating scale. And a response is defined as a 50% improvement on the [unclear]. And as you can see, Escitalopram leads to statistically significantly more responses than Citalopram. And the number needed to treat is about nine. So in other words, based on this meta-analysis, nine patients have to be treated with Escitalopram to achieve one additional response.

However, we also conducted a second meta-analysis which is presented on slide 11, and here we used data from the same studies and we were conducting a so called effect size meta-analysis and what this means is we wanted to know what the actual pool difference between the two drugs in points on the Hamilton depression rating scale. And so…

Dan Lessler: Excuse me, just for a second her. I just wanted to let people know that the slides that you're presenting on the meta-analysis are actually missing from what we're actually able to project, but we have them in our handouts. So I just wanted to let committee members know that.

Gerald Gartlehner: Okay. Sorry.

Dan Lessler: Yep. That's okay. You can go ahead. I just wanted to let people know.

Gerald Gartlehner: Okay. So I'm on slide 11. That's the effect size meta-analysis. And as you can see, in this effect size meta-analysis, Escitalopram is still statistically significantly better than Citalopram, but the actual difference is only 1.4 points on the HAM-D scale, which is a difference that is most likely not clinically significant. So it looks like dichotomizing this HAM-D scale into responders and non-responders led to an overestimation of the actual difference in treatment effect. So overall, it seems to be a slight difference in efficacy between Escitalopram and Citalopram, but it does

not seem to be clinically significant. And overall these findings did not change our conclusion. We are still saying that no substantial differences in efficacy exist among second generation antidepressants.

Slide 12 we have two more head-to-head trials for major depressive disorder and they compared to Sertraline and Venlafaxine to Citalopram. And both trials did not report and differences in efficacy.

Slide 13, for dysthymia we found one placebo controlled trial of Sertraline in elderly patients. Results did not present a higher efficacy of Sertraline in response rates and quality of life compared to placebo. We still do not have any head-to-head studies for dysthymia. Slide 14, for major depressive disorder in pediatric patients we did not find any new evidence overall. The overall grade of evidence is still poor. Slide 15, for generalized anxiety disorder we found one new head-to-head study which showed there is no difference in efficacy between Paroxetine and Sertraline.

Slide 16 we did not find any new evidence for obsessive compulsive disorder. Slide 17 for social anxiety disorder, one new head-to-head study shows no difference in efficacy between Venlafaxine and Paroxetine. Slide 18, again, no new evidence for panic disorder. Slide 19 for post traumatic stress disorder we found one new head-to-head trial and this trial did not find any differences in efficacy between Citalopram and Sertraline. Slide 20, we still don't have any head-to-head evidence for premenstrual dysphoric disorder. One new placebo controlled trial presented a greater efficacy for Paroxetine compared with placebo. Slide 21, adverse events, we included six new studies for adverse events. Overall they were consistent with existing evidence and did not lead to any changes in our conclusion and we described them in more detail in the report. One of the things was a head-to-head trial which sexual side effects for Paroxetine compared to Citalopram. And this study did not find any significant differences between the two drugs. Slide 22, likewise for subgroups we included three new studies in subgroups and these studies were consistent in their findings with existing evidence and did not lead to any changes in our conclusions. None of them was a head-to-head trial. And this slide concludes my presentation on the update. If you have any questions, please go ahead, I'll be happy to try to answer them.

Dan Lessler: Thank you. I think what we will do here first is to open up to questions for Dr. Gartlehner from members of the P&T committee, if there are any questions with respect to his presentation, points of clarification. It appears that there are no questions from the committee, so what I'd like to do is open it up for stakeholder input. And, Dr. Gartlehner, if you could stay on the line for this. And actually, I need- I don't have- the sign-in sheet. If you could get that.

Male: I'll get it for you.

Dan Lessler: Thank you. It looks like we have three people signed up. First, Mr. Mark Shigihara from [unclear]. And I was going to ask if people could be sure to limit their comments to three minutes. That would be great. Thanks.

Mark Shigihara: All right. This is switched on, right? I'm Mark Shigihara. And I am a managed care specialist [unclear], but I'm actually here today under the other hat that I wear, I am affiliate faculty members with Washington State University, University of Washington and Oregon State University's Schools of Pharmacy. And I am a specialist in evidence based medicine, and part of that role and responsibility is I get students that come in and do evidence based reviews for 4-6 week periods. Included in that has been the antidepressant class. And what they've done is they've looked at the depression class with a very practical twist in looking at this. And so I'd like to share some of their results. First, Venlafaxine is an SNRI that's serotonin-norepinephrine reuptake with weak dopamine effects also. And it has a documented safety efficacy profile over a ten year period with also 10 million patients. When Venlafaxine XR, which is Effexor XR, it has a unique documented evidence for multiple mental disorders. And when one of the practical questions they looked at was what happens post initial SSRI failure, because in real life the majority of patients go on an initial SSRI. So the question is what happens an initial SSRI failure. So in review of the evidence there is evidence within publications that indicate that Venlafaxine XR could be considered in an alternative for that initial failure. And that becomes a significance because when you look at the studies the evidence supports that if the patients do not achieve their mission on their initial therapy and continue to fail and not achieve their mission, that worsens their patient outcome down the line. Secondly, Venlafaxine is the only SNRI that is FDA indicated for GAD, SAD and panic disorder. And why that is of significance is because of the high prevalence there is between depression and comorbidity such as anxiety. When you look at the scope of things, a lot of the studies are designed to just look at depressed patients or anxiety patients separately, but when you look at it clinically, there is a lot of crossover between anxiety and depression and that's an effective point there. Lastly, from a managed care standpoint, Effexor EX is covered on all the commercial managed care plans as a formulary product and I'm just going to mention one plan and that's Regence Blue Shield that's a dominant managed care organization in the area. Upon them looking at the evidence and their formulary review, they have all generics in their Tier I, and they have an exclusive branded preferred product and that's Effexor XR in their Tier II. So, thank you for the time and I hope based upon the evidence, that this allows you to consider Venlafaxine XR for either formulary position or earlier access post an initial failure.

Dan Lessler: Thank you. Are there any questions? Okay. Next is Mr. Jeff Hill? Am I pronouncing that right.

Jeff Hill: My name is Jeff Hill. I'm from the medical of Eli Lilly and Company. And I would like to provide some comments to this committee regarding Cymbalta, which is indicated for major depressive disorder and diabetic peripheral neuropathic pain. Several publications related to Cymbalta were not included in the Oregon report and I would like to share information from these published studies with this committee. In the Oregon report both speed of antidepressant response and relapse prevention are listed as outcomes of interest. Publication by Hirshfeld reported the results regarding Cymbalta's onset of action, which showed significant improvement over placebo at the second week of therapy on the HAM-D17 total score and in response rates. Individual symptoms such as depressed

mood, anxiety and guilt showed more rapid improvement with separation from placebo at the first week of therapy. A publication by Pariah reported results from a 26-week relapse prevention study and in this study Cymbalta has a statistically significantly longer time to relapse over placebo. Treatment emergent sexual dysfunction is also reported in the Oregon report as a tolerability outcome of interest. A publication by Delgado reported results of treatment emergent sexual dysfunction in placebo and Paroxetine controlled Cymbalta trials. Results show that both Cymbalta and Paroxetine had statistically significantly greater rates of sexual dysfunction over placebo, however the rates of sexual dysfunction were significantly lower with Cymbalta in comparison with Paroxetine. Subgroup analysis based on age and race are also listed in the Oregon report as outcomes of interest. A publication by Nelson reported results on the safety and efficacy of patients lower and older than age 55, and a publication by Bailey reported results of African American and Caucasian patients. Results of these two studies show that the treatment effects did not differ significantly in these patient groups. [unclear] to talk a little bit about safety. Cymbalta's been shown to be safe and well tolerated. Commonly reported adverse events include nausea, dry mouth, constipation and decreased appetite. Cymbalta has been associated with some slight increases in blood pressure but has shown low rates of sustained elevated hypertension consistent with the class that carries the boxed warning for suicidality and is not indicated for pediatric patients. And Cymbalta should not be used with [unclear] insufficiency, chronic liver disease or substantial alcohol use. Additionally, in some patients it may take 4-6 weeks to see efficacy. And while there are no differences in safety or efficacy noted in older populations, greater tolerability issues may be existent in that population. I would like to thank this committee for its time. And also, at your request, I can provide you with the publications that I discussed. Thank you.

Dan Lessler: Any questions for Mr. Hill from the committee? Okay. Thanks. Next is Dr. Bill Schmidt from Glaxo Smith Kline.

Bill Schmidt: Thank you. Good morning, ladies and gentlemen. I am Dr. Bill Schmidt a psychiatry medical scientist with Glaxo Smith Kline. And I'd actually like to take a little bit of a different tact with the few minutes that I have and discuss an aspect of the drug treatments for depression anxiety that are not covered in the report. The report, as you know, addresses initial use of antidepressants and it looks at efficacy, effectiveness, safety, tolerability. But the third leg in the stool of treatment, if you will, is adherence, and that's not really something that's looked at in the report. There was an interesting article published last year, in August in fact, in the New England Journal of Medicine, which was not particularly provocatively titled Adherence to Medication. And it covered various medication for all manner of disease states. And one of the interesting statistics that they mentioned was that 30-70% of all US medication related admissions were due to non-adherence at a cost of approximately $100 billion. Now, among the psychiatric population it's known from several publications that about 50% of patients will stop their antidepressants within about three or four months of initiating therapy. The article did mention, among others, two major predictors of non-adherence were in fact side effects, which is not at all surprising, as well as treatment complexity, which you could consider dosing schedule as being one of them. Two strategies for improving

adherence then would be to design drugs that have better tolerability, in particular controlled or extended release formulations as well as simpler dosing. And I would point out that Glaxo Smith Kline offers two anti-depressants that fit both of these strategies in an attempt to improve adherence. The first one being Paxil CR, which is the only controlled release SSRI on the market. It was developed initially to improve tolerability and that has been shown in several clinical trials, especially those against the immediate release of Paroxetine. And regarding adherence, a retrospective study of a large national managed care database, including over 116,000 patients, patients taking immediate release SSRIs were in fact 14% less likely to be adherent over six months compared with patients taking Paxil controlled release formulation. The second drug, of course, is Wellbutrin XL, which is the only formulation of Bupropion which does allow once daily dosing. And there is even more information regarding adherence on Wellbutrin XL. There are two studies where patients were found to be 2.6 times more likely to have persistency of 70%, which is generally considered to be the minimum threshold definition for adherence. And an additional study, which looked at prescription claims data. And in the acute phase of treatment 37% of patients taking Wellbutrin XL were adherent versus only 22% taking the twice daily formulation of Bupropion. So in closing, I would reemphasize that, of course, improved tolerability and simplified dosing regimens are two strategies that can be used to improve adherence. And numerous studies have shown that adherent patients are more likely to achieve remission. They have fewer recurrences and lower overall healthcare costs.

Dan Lessler: Thank you.

Bill Schmidt: Thank you.

Dan Lessler: Are there any questions for Dr. Schmidt from committee members? Jeff, did you have a…?

Jeff Graham: [unclear].

Dan Lessler: Right. That's what I was going to do. Gerald, do you have any particular comments on what you heard?

Gerald Gartlehner: Well, I think Dr. Schmidt's points on adherence are very valid. Adherence clearly was outside the scope of our review. We looked at the comparative efficacy and effectiveness. I have one additional comment on the first person on Venlafaxine. I think months ago the results of the Star D trial were published and the Star D trial looked at patients who have failed first line treatment and then randomized into Bupropion then Venlafaxine. And that they leave Paroxetine or some other SSRI. And result of the Star D trial showed that there was no statistically significant difference in efficacy between these three drugs as second line treatment. So those are- this is the newest finding on second line treatment. But he is correct. Second line treatment is not included in our report.

Dan Lessler: Okay. Thank you. If you want to briefly comment I can give you just a brief comment.

Mark Shigihara: Yes. Regarding Star D, that is one of the latest publications regarding second line treatment and without getting into a lot of details on the study, one of the parameters was a 15% differential to reach statistical significance, but when you look at the raw numbers there was a clinically significant difference for Venlafaxine versus Sertraline, which was the SSRI that was in the study. And so that citation. And also in Star D they made a citation regarding that there was no prior evidence regarding second line utilization of Venlafaxine. There are other pieces of evidence published regarding Venlafaxine's utilization in that area.

Dan Lessler: Gerald, did you want to?

Bob Bray: This is Dr. Bray. Regarding the comment that you just made. You said that there was a clinically significant difference that fell underneath the threshold. Did you mean a clinically significant difference or a statistically significant difference?

Mark Shigihara: It was not statistically significant from the 15% differential that they were looking for, but the numbers would have reflected a clinically significant- it was a 17% versus a- between a 23 and 24% differential between the products.

Dan Lessler: Gerald, did you- I don't know if you wanted to comment further at all.

Gerald Gartlehner: I'm not really familiar with the exact numbers in the Star D trial, but I just have the overall message in the back of my mind that there was no…

Dan Lessler: No difference, okay.

Gerald Gartlehner: statistically significant difference. And I can't really comment on the clinically significant differences.

Dan Lessler: Thanks. Any other? Yeah, Angelo.

Angelo Ballasiotes: Question- this is Angelo Ballasiotes. Questions come to mind with regards to suicidality, especially in children, with regards to antidepressants. Is there any new data available at this time? Or…

Gerald Gartlehner: Is this a question to me?

Angelo Ballasiotes: Yes. Excuse me.

Gerald Gartlehner: Well, a large systematic review was conducted in the UK by Safety of Medicines [unclear] there, and there is no comparative data on second generation antidepressants out there. Their findings were that second generation antidepressants probably have an excess risk of self-harm. They did not find any differences in actual suicides. But suicidality as a self-harm suicidal ideation might be increased. The problem is that the event rates are very low, so all the clinical trials usually are too small to really show any differences. And they aggregated data from published and unpublished randomized control trials. And also

observational data. But they also could not come up with any conclusion about the comparative risk of suicides among second generations antidepressants.

Dan Lessler: Thank you.

Patti Varley: This is Patti Varley. While we're talking about adherence, the other issue that's come up is the issue of withdrawal, especially with the fact that there are people that don't respond to initial treatments. Do you have any information about the problem, for instance, that there's a higher instance of withdrawal difficulties with Paxil versus the others? Was that in your database? And then just for point of clarification, wasn't there some production problem with Paxil CR at one point and therefore access was limited for a while?

Bill Schmidt: Yeah, those are both very good questions. And to answer the second one first, the production problems surrounding Paxil CR have been taken care of and the drug is now back in general distribution. And the first question again was?

Patti Varley: The withdrawals.

Bill Schmidt: Yeah, the withdrawal symptoms. Yeah, generally speaking when one looks at the SSRI class, if you take into account all the studies that have been out there, it seems pretty clear that the withdrawal symptoms, what you're seeing with them relate more to the half life of the drugs than any other given thing. And nonetheless, all of the advice given for the drugs as far as I know is that if you are going to discontinue them you must do a very- a slow down titration and slow forth. If you are switching to a different SSRI there's probably less importance placed on that slow down titration. That is you can be coming down on one and up on another with less time intervention between the two. I don't know if that answers your question. Okay.

Dan Lessler: Thank you. Patti, did you want to comment, too, on that…

Patti Varley: [unclear].

Dan Lessler: Gerald, could you comment on either aspects, or…

Gerald Gartlehner: Well, in the report we pooled discontinuation rates from included efficacy trials and overall we found that there are no statistically significant differences in overall discontinuation rates between- we took SSRIs as a class and then Venlafaxine, Bupropion, Mirtazapine. When we looked at discontinuation rates because of adverse events, Venlafaxine has highest- significantly higher discontinuation rates than SSRIs as a class and the reason probably is that Venlafaxine has higher rates of nausea and vomiting than SSRIs. It has to be kept in mind that these are efficacy trials and they are- these are results in a highly controlled environment. So the adherence inside these trials and discontinuation of side trials in the real world circumstances might be different.

Dan Lessler: Thank you. Any other questions? All right. Well, I think we're all set. We can let you go. We appreciate your time and assistance. Thanks a lot.

Gerald Gartlehner: Thank you.

Dan Lessler: Bye-bye. Actually, as we sort of move towards a motion or a recommendation here, what I thought would be most useful if we could look at what our last recommendation was and a number of months ago, I think we did this in December

Male: It's on page…

Dan Lessler: Which page?

Male: 22 of the tab that says drug review history.

Dan Lessler: Ah, there we go.

Male: Dr. Lessler?

Dan Lessler: Yeah.

Male: I just want to make a comment just for general information that adherence is a big issue. The Puget Sound Health Alliance with the Depression Committee is looking at adherence and they're going to be coming out with some recommendations how to improve that in the state of Washington.

Dan Lessler: Thanks. Actually I'm looking for the- oh, there we are. So maybe if committee members just want to look at the previous recommendation- and was that in July of 2005 that we- I thought it was- was that- I thought…

Male: I think that's the implementation date of the antidepressants.

Dan Lessler: Okay. Thanks. To review the last time when we had reviewed this and made a recommendation the recommendation read that Citalopram, Escitalopram, Fluoxetine, Sertraline, Fluvoxamine, Paroxetine, Mirtazapine, Venlafaxine, Bupropion are safe and efficacious. The PDL must include Fluoxetine, Citalopram, Mirtazapine and Bupropion. The second generation antidepressants shall not be subject to therapeutic interchange for the treatment of major depressive disorder. And then I think also included for MAA just your algorithm on- is that correct, Jeff, here- we're at the refill flow chart. Can you remind me- I looked at that and now I don't know what- which tab or what page that's on.

Jeff Graham: Refill flow chart.

Dan Lessler: There we go. So people can take a look at that as well. So with- noting the previous recommendation and having the opportunity to look at the algorithm for refills, at least with respect to MAA, wondering if there's any general comments at this point.

Angelo Ballasiotes: This is Angelo Ballasiotes. I noticed that Sertraline is not on the approved drug list. And it's coming off patent here, I think in several months or a couple months.

So I wondered if it would be a consideration of including that or at a date when it would come off patent.

Jeff Graham: This is Jeff Graham. We tend to wait until it comes off patent because we've been promised things are coming off patent in the past and that was a year and a half ago or maybe two years ago with some drugs. And so we tend to wait until that happens. And if, you know, if it says that it's safe and efficacious, we would follow the pricing and so forth and could bring it on at a certain time but basically we don't do that in anticipation that it's going to come on, because we've been fooled.

Dan Lessler: Right. Bob?

Bob Bray: Bob Bray. I recall some of the discussion about our recommendations for what drugs should be on the PDL, and they were based on relatively unique factors of the drugs. And as I recall, we were citing Citalopram as needing to be on there due to issues that had to do with fewer drug/drug interactions. Of the evidence we're looking at today it doesn't look like that is something that necessary fell out of the evidence. And then the new evidence is the new efficacy information between Escitalopram and Citalopram. But it seems that, I guess from my perspective, the issue about Citalopram could also be linked with Escitalopram and Sertraline in that the length of… (end of side A of tape 1)

Bob Bray: …driven by maybe a practical approach to what to do when there's failures.

Dan Lessler: Any reaction to Bob's comment. Patti?

Patti Varley: This is Patti Varley. Yeah, I think the hard part is when you look at all of the evidence that's presented. It's hard to show that any one in particular sticks out as being safer or efficacious. And I think that even this- the data about initial failure and what works secondarily is also very vague in regard to response rates. So I think it's tough to say that anything sticks out as having clear evidence of either- you know, I think that there are some good points here about other things to look at in regard to adherence, etc., but we don't have that at this point.

Dan Lessler: Bob?

Bob Bray: This is Bob Bray again. A question, I guess, about the prior authorization issue. Just following the flow chart, and let's just assume it's an endorsing provider and the endorsing provider wrote for an SNRI but did not sign DAW, so therefore that would be- if it wasn't a refill that would be kicked out as needing prior authorization. Is that right, Jeff?

Jeff: So it's an endorsing provider, did not write DAW, I believe it's an SNRI here, which [unclear] they write for a non-preferred or a preferred?

Bob Bray: There's not an SNRI that's preferred currently. Correct?

Jeff: If it's non-preferred and they don't write DAW, then it would be a PA.

Bob Bray: I haven't had to do that, so what would we- I mean, just for the standpoint of knowing what would be convincing on a PA that would enable that to be approved? What are the criteria?

Jeff: I can only give you examples when I talk to psychiatrists where they have multiple comorbid conditions and they can make the argument- I just talked with somebody- depression, anxiety disorder, bipolar and- what else did they have? ADD. This one woman. Well, we want to slam 'em with a lot of serotonin, so I want to have this SNRI and this SSRI so I can cover all my basis. And fine.

Bob Bray: So it's a case by case review, not necessarily set criteria for the prior authorization.

Jeff: And when we've looked at sort of algorithm approaches and things like that I think we can get it down to a documented treatment failure. And the new WAC I just basically say if it's sort of C rated evidence; show me it's less risk, less cost to the state, next step in reasonable care, I'm fine.

Dan Lessler: Okay.

Jeff: I'm trying to get it out, but I do believe though that the DAW and non-preferred is fairly brisk in this drug class. I don't have it up, but it's somewhere in the 40-50% range so the DAW is working very well.

Dan Lessler: Are there other…

Jeff: The other thing that [unclear] reminded me is it document next step and reasonable care, show me that they've tried and failed two of the preferred agents would be an indication. Because you've got some options there. You jump to an SSRI or SNRI.

Dan Lessler: So I think just going back to the previous recommendation, just to emphasize I think just what Bob was saying that the basis for that recommendation was No. 1 to assure that there would be available on the PDL a number of different antidepressants for all intents and purposes I think different mechanisms of actions. I suppose we can put that in quotes. No. 1. And then I do recall the discussion about Citalopram as well in terms of metabolism and drug/drug interaction. So that's how we got to the recommendation. I think the point that Bob brings up now is whether or not we in fact are the one covering the range of potential mechanisms of action. It seems that there is one that is missing. And whether or not in light of evidence we are hearing today we should- we would want to make a change. And then as well, whether there is any need to specify Citalopram with respect to drug/drug interaction. So, with respect to the first that does seem to be the two issues for discussion. With respect to the first, I'm wondering if there's any comment. Talking about an SNRI, which is- would be absent from the previous recommendation. If people want to speak to that either way. Look particularly at our mental health experts here, Angelo and Patti, whether…

Patti Varley: Not sure I'm clear on what you're asking.

Dan Lessler: What I'm asking is that I suppose- was I not- the question is the point- Bob has raised two points to sort of put out here for further discussion. The first point had to do relative to our initial recommendation that we had- that the rationale for that recommendation, if you look at it, was to assure that the PDL had a breadth of antidepressants on it that- which represented different mechanisms of action in some respect. And the question is the breadth that is recommended, that's included in that previous recommendation appropriate, or is there reason to add an SNRI. I guess that's the question.

Angelo Ballasiotes: I'm Angelo Ballasiotes. Is that with regards to the preferred list?

Dan Lessler: I think what we did in our previous recommendation is we actually specified. We said, for all intents and purposes these medicines are efficacious and safe when used appropriately. There are certain medicines that need to appear on the PDL because we want to assure a breadth of options, which was driven by consideration of mechanism of action. Having different mechanisms of actions available.

Angelo Ballasiotes: Well, I agree with Bob because it's kind of cumbersome now being a [unclear] and prescribing. It's difficult to- well, it's time consuming to give out of the SSRI when you want to add another medication that has a different mechanism of action. And I think clinicians when they look at prescribing they look at mechanisms of action and how they're going to work possibly with their patients. We have somebody with a real low energy level and you're gonna probably make an educated guess that maybe an SNRI would probably benefit that person a little better than just an SSI. You're not going to get the full impact of the antidepressant with just possibly one mechanism of action.

Dan Lessler: Patti?

Patti Varley: I guess- I hope I'm answering your question again this time. This is Patti Varley. Is that again, my feeling is that when you look at the evidence presented as far as efficacy and safety and you look at what was just being referred to, which is the breadth of the variety of patients that we're looking for response in, there isn't a way to predict which medications are going to be the most beneficial to an individual patient. And when you look at safety and efficacy, they don't stand out as one versus the other having strong evidence one way or the other.

Bob Bray: This is Bob Bray again. A little side conversation with Jason. He was pointing out that in our initial statement of what are safe and efficacious, we did not have Duloxetine reviewed previously, so we probably want to add that. And we specifically left off Nefazodone because of the rare toxicity issues, which again may be difficult to quantify in the data yet it's a rare but very significant safety issue. And the other thing might be that when we talk about SNRIs in a reviewing how they're grouped at the beginning of this report, when I'm thinking of an SNRI I'm thinking of Duloxetine and Venlafaxine. And even though others have both- Mirtazapine is in there and Nefazodone is in there as having some dual action, I think it may be helpful if we just identify SNRIs as being one of those two drugs.

And I don't know if that helps in the discussion, but it helps me thinking about how we're grouping them anyway.

Dan Lessler: Thanks, Bob. And that is an important point that Duloxetine was not considered. So that is under consideration here. And, Patti, if I'm correct, what I hear you saying is that it doesn't seem like there's compelling evidence from your standpoint to change the existing recommendation. Just- that- actually, I was wondering- Dick Mioshi is here, Dr. Mioshi. Have to put on my other glasses to see him. And Dick, you were a consultant when we had this discussion, so I just- I hope you don't mind, I just wanted to turn to you and see if you had any comment with respect to this specific question.

Dick Mioshi: Well, clinically what we do is if you either have sexual side effects, so on and so forth, then you have to have another option. I'm not sure if the effects are at low dose, which looks more like an SSRI helps you that much, but on the higher end, when you run into the 60 or 80 mg Citalopram so on and so forth then you get a failure, you go to another SSRI. If you get no response then you jump class. Then you run out of drugs really fast because then you have Bupropion and then where do you go after that on our list. So there's probably a need for an SNRI. Unfortunately all the SNRIs are all branded. The Duloxetines, Venlafaxines, and we may have another one in the future, but that won't probably be for another couple of years. So it gives you an option that you- and that's where we usually go. We've talked about this the last time that we- in the last meeting about where to go after you have a single neurotransmitter agent. You have to have a place to go without- and I mean, the argument is if you sign DAW then you can do whatever you want. But what happens to the other [unclear]. And that was the- as far as the chemistry goes, essentially you need another option.

Janet Kelly: This is Janet Kelly. I just had a question now about if you've tried an SSRI on the list and Bupropion, that is kind of an easy- if you've tried it and failed, though, even if you're not a dispensing prescriber that you can have it at that point. Because you've tried and failed too. So my question, I guess, is since this isn't my area of practice, if you're starting someone that you know [unclear] this is the first thing, I mean, in my experience it's usually an SSRI. And then if they don't respond to that, what's your second option?

Dick Mioshi: The way it is now you would probably go to Bupropion. Then unfortunately if you have panic anxiety then you have to think twice about it because it's mostly serotonergic drugs that work for panic anxiety. Which makes it a little sticky again. I hate to sound like I'm selling Effexor, but it is actually serotonergic at low dose then you get more of a balance at higher dose. So actually you can use it and they do have the indications for it. So that's part of the argument that we run into.

Janet Kelly: But again, my question would be that if you've failed it and you could access it, or if you DAW it you could access it, it would still be something you would get to there as opposed to starting with.

Dick Mioshi: Probably yeah. I mean, clinically we hardly ever start- but most of my guys come after four or five failures on other things, anyway.

Male: I just want to remind people as well that the decisions affect other state agency formularies. So, for example, Uniform Medical and it might be helpful just to understand how a recommendation, again, one way or another affects the structure of the Uniform Medical Formulary with respect to these medications.

Donna Sullivan: This is Donna Sullivan. How they are right now our Uniform Medical plan our Tier I is all generic products. Tier II would be the preferred brand name products and Tier III would be non preferred brand name drugs. So currently the drugs that we have right now are all generic so they're all Tier I. With the- in regard to Venlafaxine, it's a non preferred drug, so if you have an endorsing provider that writes- and actually we don't even reject it for therapeutic interchange because you said that they're not subject to therapeutic interchange, so it gets processed regardless if there's a DAW or not. But it is a Tier III drug.

Patti Varley: This is Patti Varley. And even if we added it in it would remain a Tier III drug?

Donna Sullivan: If you required it to be on the Preferred Drug List it would be moved down to Tier II because then it would be a preferred product. I mean, it's covered right now it's just the enrollee pays more than they do for a preferred brand name drug or a generic product.

Angelo Ballasiotes: This is Angelo Ballasiotes. In some times in some occasions we wind up with two drugs so we can get the mechanism of action. We wind up with Bupropion and an SSRI to achieve the goal that we want to achieve with a multi mechanism of action. So the question is do we want one drug on board or two.

Jeff Thompson: And would you allow that? When we have issues is when there are two SSRIs, which we found in quite a significant amount of people, or combinations that don't necessarily make clinical sense and that's where we publish the two by two table for combinations working with the Mental Health Work Group?

Dan Lessler: Other comments at this point?

Male: When we look at the chemistry and we go, Okay, SSRI plus Bupropion gives us Effexor. But, you know, in this world of data there's no data because nobody's going to do that study. And so it's all kind of clinical lore that we think is going to happen. A lot of those also people are doing the additive Bupropion for sexual dysfunction, which you wind up just changing them over to Bupropion anyway. So they get just one of those stuck in the cross kind of things.

Male: If it works.

Male: And sexual dysfunction is a big issue, too.

Male: We started out with 15% with Prozac and by the time we got to the last SSRI and we actually asked the question it was closer to 50.

Dan Lessler: So, are there any other comments on this? Thanks, Dick, I appreciate it. Maybe before trying to craft a recommendation here we should just continue to the next issue that Bob brought up and whether there's any discussion just around the Citalopram, please. There is somewhat of a less complicated question, but it was there because the thinking was that it had fewer drug/drug interactions. And I was wondering if anybody- if there was any comment one way or another on that. Bob's observation is I think looking at the data and questioning whether or not that's- whether that's a valid assumption. We need our pharmacokineticists here.

Janet Kelly: It doesn't appear- this is Janet Kelly. There doesn't appear to be any new data, but the other question I have is it's generic now so I'm not really sure that it's a big issue. At the time I believe it was not a generic product and so we had to call it out specifically. But…

Male: Actually, I think it was a generic product.

Janet Kelly: It was generic?

Male: Yeah, it was.

Dan Lessler: Any other comment? Jason, I'm wondering if you have any specific comments. All right. So, at this point is- would there be a recommendation just to begin with, not a motion, something we could all maybe take a look at as a starting point here? Again, it really seems like the key difference comes down to the SNRI question and whether or not we want to change the recommendation previously.

Patti Varley: This is Patti Varley. And I guess I feel like you asked me a question and I may have responded where I wasn't clear, or as I'm looking at this saying again that if you look at the review that we just did, the issue of eliminating it seems unreasonable if we're looking at is it equally safe and efficacious. That was my point earlier.

Male: And it's more with respect to if you look at the old- the prior recommendation, it's the second line, so to speak, that whether the PDL should specify inclusion. So I think…

Patti Varley: Right. And is that no longer what I'm being asked to do, right? Or is it still- I guess that's where I get confused sometimes about the question at hand or the specific answer to some of these questions.

Dan Lessler: 'Kay. Bob, I'm wondering if you want to give a try to just something maybe building off of the prior recommendation.

Bob Bray: Yeah. Bob Bray again. The- I guess in comment to Patti's comment just then. I'm reading here in the body of the note that says that- this is a quote "it concluded that the SSRIs are not equivalent in their potential for drug interactions and that each combination must be assessed individually. The authors also noted a general trend in which compared to other antidepressants Citalopram and Sertraline appeared to have less propensity for important interaction." So pretty soft comments and I

guess it almost seems like the drug interaction thing is kind of- maybe something that should be off the table. So I'll make a stab at a suggestion. This isn't neces- don't type this yet, but…

Male: It's going to help us to have it up there to look at.

Bob Bray: All right, fine.

Male: Okay.

Bob Bray: Okay. So as a stand I would say- can we go back to the- After considering the evidence of safety, efficacy and special populations for the treatment of major depressive disorder, I move that Citalopram, Escitalopram, Fluoxetine, Sertraline, Fluvoxamine, Paroxetine, Mirtazapine, Venlafaxine, Duloxetine and Bupropion are safe and efficacious. Then the PDL must include Fluoxetine, Mirtazapine, Bupropion and at least one of the following: Citalopram, Escitalopram, Sertraline and/or Paroxetine. And then I would leave the last part about not subject to Therapeutic interchange.

Dan Lessler: Thanks. So just looking at this as a point of discussion…

Female: Do you want this sentence that says no single genera- no second generation antidepressant medication is associated with [unclear] side effects?

Patti Varley: I'm not- this is Patti Varley. I'm not sure you can leave that in there if you're leaving out Nefazodone for that reason. It just- that doesn't flow right in my mind. Because you're saying you're leaving it off, right? Indirectly you're saying you're leaving it off because of the liver toxicity, right?

Bob Bray: Bob Bray again. I guess what I'm saying is that yeah, indirectly we left it off, which then means that of the drugs that are mentioned none of them would stand out. But I think it's perfectly reasonable, given how we've stated it, to leave the sentence out as well.

Patti Varley: And I'm gonna- this is Patti Varley again. I'm just gonna do this because I need to clarify it in my own mind. If your first sentence of I move that that whole list are safe and efficacious, and then your second list of what must be on the Washington Preferred Drug List, how did we get from the first list to the second list?

Bob Bray: Bob Bray again. The- in my mind, the reasons to specify those is Fluoxetine is somewhat unique in its long-acting nature without regard to whether or not its special formulation. Mirtazapine is unique in the sense that it does have mixed effect and probably more importantly it does have the significance of adding weight particularly, which some people don't want that, but one person's side effect is another person's benefit. Bupropion because of the sexual side effect issues. And then the grouping of the next four, primarily because those are less long-acting SSRIs that because they're pharmacologically different than the prior three, having at least one of those would make sense from a subclass choice issue. That's my rationale.

Dan Lessler: Any other questions about how this is currently formulated as a recommendation?

Patti Varley: Well- this is Patti Varley. I understand the clinical logic of that. Again, I'm struggling with based on the clinical evidence. The list to me is the list and I haven't seen anything here and I do think, again, if I take my hat off from the evidence based thing to a clinical thing, there is those issues that you just mentioned but I think if you leave the list then that's how you make the decision. I'm struggling with this.

Bob Bray: Bob Bray again. My concern, I guess, if we just said they're all safe and efficacious and then let the rest of the process flow, I'm concerned that what could happen is we could wind up with one drug. And because of the fact that these drugs have pharmacologic differences, even though I agree with you, Patti, that there doesn't seem to be anything in the evidence that specifically separates them on an initial prescription basis, I'm concerned that we preserve some degree of choice that's based on if not evidence then at least rational prescribing.

Donna Sullivan: This is Donna Sullivan. If you don't want to name the particular products- I think where Patti seems to be going, you could just tell us how many products, unique drugs we have to have on the Preferred Drug List in order to allow choice as opposed to naming particular drugs. And then the cost analysis determines which ones come out as preferred. Like right now, if some of these medications were less expensive than the ones that you particularly named, they would be included on the list because it wouldn't make sense to steer people towards more costly medications when less expensive ones are working for them.

Patti Varley: So this is Patti- I agree, Bob, with you in regard to we need- I mean, if that were the case where we could say that and then end up with one drug, that to me is problematic. In that we absolutely need to have a statement in there that there needs to be a range. But I'm struggling with how to say that in that balance.

Ken Wiscomb: Ken Wiscomb. I think I'd like to take it one step farther and sort of look at it the other way. While the first group of drugs are clearly safe and efficacious, it seems to me that if we want to offer choice in the second grouping then we really out to be- to be consistent we ought to add [unclear] and then the last grouping would make sense [unclear] because we're looking for a shorter [unclear].

Dan Lessler: Carol?

Carol Cordy: Carol Cordy. I agree where we could add "and must include an SNRI." We kind of tabled that. And I wasn't sure where we were in wanting to do that or…

Ken Wiscomb: I just think we need to have an SNRI in there so we represent the entire [unclear]. Seems like we're representing three out of four as it is now.

Carol Cordy: But I think it would have to be another addition. It couldn't be lumped with those medications.

Ken Wiscomb: You take it- I'm sorry.

Carol Cordy: I mean, you'd have- it'd have to be one of the following and one of the following.

Ken Wiscomb: Well, that could be. That could be.

Male: So, another way to go with this, to Donna's point- and which I think might meet the objectives that are being raised here would be- actually just to specify sort of within sort of the subclasses of SSRI- you know, an SSRI and an SNRI must be on the formulary. And I don't know what to do with the other category. Maybe we could actually specify potentially by name. So, and within SSRIs I think this is- well, for Fluvoxamine I would agree with Bob in terms of its duration.

Male: And just a brief addition on that. The other reason to have Fluvoxamine in there is because it is the only one that is been shown to have the effectiveness versus risk analysis for kids. That was the other reason.

Dan Lessler: Right. That was the other one. So, what if we kept the first sentence, which just speaks to the fact that safety and efficacy across all the medicines and then specified that the PDL must include at least- must include at least two SSRIs, one of which is Fluvoxamine, an SNRI and here I would probably just say Mirtazapine and Bupropion, since really there's nothing different from the last time we looked at this and there's good reason to include those medications in terms of the breadth of options and they're generic and so on and so forth. So, how does- huh? So how does that- that gets at the issue of trying to speak more- more globally in terms of subclasses and medicines but also making sure certain types of specific medicines are available on the PDL. Is there any comment on that as a way of putting this together then? I think the big difference here relative to our previous recommendation is it actually specifies availability of an SNRI and does not specify Citalopram specifically.

Bob Bray: This is Bob Bray. I support that.

Dan Lessler: All right. So.

Patti Varley: We had our little side- this is Patti Varley. Side conversation. And I'm just curious, where is Trazodone?

Dan Lessler: It's not an SSRI. I mean, it's not…

Patti Varley: I know it's not an SSRI, but it's an antidepressant.

Dan Lessler: I think it's not being considered amongst the medicines that we're considering today. So it's…

Male: Well, should it be on there?

Dan Lessler: No.

Donna Sullivan: Excuse me. This is Donna Sullivan. It is considered a first generation antidepressant. These are the second generation antidepressants.

Dan Lessler: So, to move us along- actually, Bob, I'm wondering if you would be willing to read this and put this forward formally as a motion.

Bob Bray: Bob Bray again. After considering the evidence of safety, efficacy and special populations for the treatment of major depressive disorder, I move that Bupropion, Citalopram, Duloxetine, Escitalopram, Fluoxetine, Sertraline, Fluvoxamine, Mirtazapine, Paroxetine and Venlafaxine are safe and efficacious. The Washington Preferred Drug List must include at least two SSRIS, one of which must be Fluoxetine. At least one SNRI, Mirtazapine and Bupropion. The second generation antidepressants cannot be subject to therapeutic interchange on the Washington preferred drug list. I so move.

Dan Lessler: Is there a second?

Male: Second.

Dan Lessler: Okay. Any further discussion? All right. We'll go ahead and vote. All those in favor please say Aye.

Many: Aye.

Dan Lessler: Opposed same sign. All right. The motion passes. And I think what we can do is adjourn until- did you want 'til 20 of or quarter of? Do you have people scheduled for the antipsychotics? Or…

Male: We have 10:45.

Dan Lessler: 10:45. So we have about little over 25 minutes and we'll be adjourned promptly at 10:45. Thanks. (end of side B of tape 1)

Dan Lessler: We're going to be- we're going- we'll be putting a sign up sheet for people who want to comment for stakeholder input back out on the table just outside the room. So if people haven't signed up we'll be- we're going to put it back up there and people will have a chance to sign up. I do want to remind everybody that they should please sign up if you want to give stakeholder comment. So we're just going to move it outside here so we can get going. And we're going to reconvene here to talk about the atypical antipsychotics. Jeff, is Marian going to be- or who's- …

Marian McDonagh: I sure am.

Dan Lessler: Marian, are you there?

Marian McDonagh: Yes, I am.

Dan Lessler: Ah, great. Welcome back.

Marian McDonagh: Thank you.

Dan Lessler: So, we're basically operating the same way we have in the past, Marian. And we have your PowerPoint presentation projected and right now we're all looking at the title slide. And so you can- you should feel free to take it from there. Now, before you get started I did- will you be able to stay with us for a bit after your presentation, Marian, to answer- just answer some questions?

Marian McDonagh: Sure.

Dan Lessler: And I think it looks like we're going to have quite a bit of stakeholder input. And so I think we won't have you stay on beyond just the questions from the P&T committee.

Marian McDonagh: Okay.

Dan Lessler: Also, I just wanted to introduce to the people who are here Dr. Sharon Farmer who is here as an expert consultant to the committee working under contract to the Health Care Authority. And Dr. Farmer is the medical director for the King County Regional Support Network and a staff psychiatrist at Compass Health, which is a community mental health center serving Snohomish, Skagit, Island and San Juan Counties. So, Dr. Farmer, I want to welcome you and thank you for being with us.

All right, Marian, I think we're all ready. You've got your title slide up there and you can take it away.

Marian McDonagh: Okay. So the drug class review on atypical antipsychotics we have updated the original report. We just concluded the update in April. In mid-April it was finalized. So [unclear] as far as [unclear] goes. Go down to the next slide- excuse me. The methods are exactly as we usually do as far as searches and quality assessments and things like that. Going to slide three. The original report included outpatients with schizophrenia, schizophrenia-related psychoses, bipolar disorder, behavioral and psychological symptoms of dementia. And then for children autism, disruptive behavior disorders and ADHD were indications that we were looking at. On the next slide all of the drugs were available were available [unclear] included reviews. And for outcomes we were focusing on long-term health outcomes [unclear], but we were also looking at some immediate outcomes, which are measures severity of illness, response, relapse, things like that.

On the next slide I will just tell you what some of the changes were from the original report to the update. We expanded the population to include inpatients. We also [unclear] interventions. So instead of just the oral drugs and long-acting injections. We also included short-acting injectables and of course all liquid formulations; oral formulations of the drugs. Then we also added studies to the report which expanded looking for more effectiveness evidence, to observational studies for evaluating the effectiveness. Previously we had a restriction of 6 months exposure time for looking at long-term harms of serious adverse events.

And we took that restriction off based on what we had learned from the original report. And we just did summarize our update searches through the end of March last year.

On the next slide a brief summary of the overall findings. Over 300 studies included. A lot of head-to-head trials. And you've all looked at a lot of these reports that we've done and 54 is a pretty large number. So we have quite a lot of head-to-head evidence here. Including observational studies, excluded the body of evidence quite a lot. 169 observational studies. And this is a topic that, as you all know, has been reviewed many times before. So we did look at those other systematic reviews quite carefully. There are a lot. We found 22 overall that are fair to good quality. But, you know, when you look at those a lot of them are very similar to our findings with the exception of that our data is much more recent for most of these. For example the [unclear] the [unclear]. And, of course, most of [unclear] included observational studies for effectiveness. So I think based on most of these [unclear] these reviews are [unclear] are outdated at this point.

On the next slide I just want to just briefly introduce the three effectiveness trials and we'll talk about them more in detail later. But there was only three effectiveness trials in this report. And those three are the CATIE trial, which included Olanzapine, Risperidone, Quetiapine, and Ziprasidone. And in this report Phase I is included. Phase II was published after the report was finalized. We also have another 12-month pragmatic trial of Olanzapine versus Risperidone compared also to older drugs. But it was a much smaller trial. It had a very high drop out and [unclear] follow up rate. So we [unclear] certain. We also had a much more [unclear] population than in [unclear] trials. The third effectiveness trial is the InterSept trial of Clozapine versus Olanzapine looking at patients at high risk for suicide. And then we had those 54 efficacy trials, head-to-head trials. And 24 of those were added in the update, which really reflects the expansion of the inclusion criteria to include other patients.

On the next slide this is the summary slide for what was Olanzapine versus Risperidone. This is really where the bulk of the evidence is in the whole report. There are two effectiveness trials [unclear]. There are also 19 head-to-head trials; 12 in outpatient, 7 in inpatient. And quite a lot of observational studies and active controlled studies or placebo controlled that we [unclear] comparisons wherever we could.

On the next slide looking at direct evidence of effectiveness, so the effectiveness trials; the CATIE trial- in the CATIE trial was Olanzapine versus Risperidone comparison discontinuation for any cause was the primary outcome measure. [unclear] there was a significant difference between Olanzapine and Risperidone with Olanzapine having a lower rate of discontinuation, [unclear] treat is 10. The time to discontinuation is the other primary outcome measure and this was also a longer time discontinuation for Olanzapine compared Risperidone. Other outcome measures that were reported had discontinuation for lack of efficacy. Again Olanzapine was superior [unclear] was 8. Time to discontinuation was also longer. Duration of successful treatment: three months versus one month. And that was statistically significant. There were no differences on the PANSS or the CGI

[unclear] so there was [unclear] of symptoms. The other effectiveness trial was the Jerrell Trial and as I mentioned it is a lot smaller and higher loss to follow up. And probably the biggest thing is that it is a different patient population. Patients had to be hospitalized to [unclear] this study initially and then it went on from there to [unclear] outpatient study. And so it's really quite a different study. This study found no difference between drugs. But [unclear] is probably the biggest reason for not being able to find difference between [unclear].

On the next slide, moving on to the observational evidence for effectiveness, we found quite a few of these studies although as you can see almost half of them are poor quality. So looking at the best of the [unclear] the studies of outpatients, Olanzapine resulted in 32 more days of treatment than Risperidone in one study. In another study known as the Drug Attitude Inventory and also physician assessment of compliance [unclear] Olanzapine superior to Risperidone. On the flip side are inpatients series of studies that were conducted in different countries [unclear] that pooled the data [unclear] says that for the moderate or shorter inpatient stay was Risperidone or Olanzapine for five days shorter. And then the difference in time to onset of efficacy also favored Risperidone. [unclear] shorter. And Pooled risk of discontinuing due to lack of efficacy also favored Risperidone in an inpatient setting, although the NNT is fairly high [unclear] 30.

On the next slide going into the efficacy trials for Olanzapine, these are very short-term trials; 12 in outpatient, 7 in inpatient. These studies did not find differences based on symptom measures. So the [unclear] as the measures of [unclear]. So responses, withdrawals, quality of life, functional status, [unclear]. Other inpatient studies; sleep quality, aggressive behavior, there were also no differences between drugs. There was, however, one trial- what I have on the slide is incorrect, it's one trial that found Olanzapine superior to Risperidone in response maintenance. And that was one of the two largest trials of Olanzapine versus Risperidone.

On the next slide looking at indirect comparisons we found quite a few active-controlled trials that reported effectiveness outcomes. However, [unclear] was reported as [unclear] outcome. So quality of life was really the only measure that [unclear] across the trials we found no difference. The quality of life [unclear] Olanzapine and Risperidone. Then we had a nice number of other types of observations that we were looking at, but because of the big difference of [unclear] report outcome measures or [unclear] measures they're measuring, really there was no [unclear] possible there.

On the next slide looking at adverse events comparing Olanzapine versus Risperidone, first of all looking at [unclear] symptoms. From the direct evidence, the head-to-head trials, 5 trials found no difference between drugs, but two did find higher risk with Risperidone, particularly looking at Parkinson type adverse events. But in those cases the dose of Risperidone was higher than 5 mg. [unclear] dose related in fact. There was one cohort study that found that both drugs have a lower risk than Haloperidol, but didn't directly compare them and the [unclear] of data that were presented we couldn't do our own analysis to compare them. But looking at the risk across them it did not appear there is a big difference between them. Looking at metabolic adverse events, four observational studies that evaluated

these; hyperlipidemia there were mixed results from two case-controlled studies meaning that one found a higher incidence of hyperlipidemia with Olanzapine versus Risperidone and the other found no difference. In glucose intolerance, again, both drugs were found to have an increase compared to Haloperidol but not necessarily compared to each other.

On the next slide, looking at adverse events evidence from the CATIE trial the rate of withdrawal due to adverse events was higher in the Olanzapine group compared to the Risperidone group with a risk difference of 8.6% and an NNT of 12. The time to withdrawal due to adverse events there was no difference between drugs however. In looking at inpatients to pool risk of discontinuing due to adverse events during inpatient stay there was a higher risk with Olanzapine and NNH again was much higher at 65. And part of that is because inpatient studies are much smaller, even pooled, than the CATIE trial.

On the next slide, comparing evidence for weight gain with Olanzapine versus Risperidone. Looking at direct evidence the effectiveness trial CATIE, the difference found there was a greater increase with Olanzapine of 3.9 kilos and a risk difference of 16%, which is a NNT- or an NNH of 6. I didn't want to pool that data with the short term trials because the duration of treatment was so different between them. However, the findings are really quite similar when you pool the six short-term efficacy trials that reported weight. The weighted mean different between weight gain and the drugs is again just over 3 kilos. Greater with Olanzapine. And a risk difference of 13% with a NNH of 8. Then looking at cohort studies, these were a mix of retrospecting and prospective cohort studies so the quality of the data might vary from which method they were using. The weighted mean difference here is quite a bit smaller, it's close to 2 kilos with a risk difference of 23% and the number needed to harm of 4.

On the next slide looking at the evidence for diabetes, the risk of developing diabetes comparing Olanzapine to Risperidone. There were eight retrospective cohort studies evaluating this outcome. Three of four studies that were making direct comparisons between the drugs found an increase risk with Olanzapine compared to Risperidone. And this included the largest and probably one of the better quality studies in this group. Not all of these increasing risks are significant, but the relative estimates were all greater than one. Now looking at the other studies, the other four studies when making comparisons not to each other, so not comparing the drugs, but comparing to patients who received no drug treatments. And these four of four studies found that Olanzapine had a significantly higher risk compared to no treatment while Risperidone did not. Additionally there was one study that looked at the risk of diabetic ketoacidosis and it was a retrospective study. And here the odds ratio of Olanzapine versus Risperidone were significantly elevated. An odds ratio of 3.5.

On the next slide summarizing the evidence comparing Olanzapine to Risperidone. Olanzapine has lower discontinuation rates, longer time to discontinuation, a longer duration of effective treatment than Risperidone. Three differences in efficacy were found. The only significant difference was in the [unclear] trial with Olanzapine having lower relapse rate. Olanzapine has a higher rate of

discontinuation due to adverse events than Risperidone among outpatients, but no difference in the time to discontinuation. And withdrawal due to adverse events in inpatients was also higher with Olanzapine. Evidence suggests that Risperidone causes more or worse EPS adverse events compared to Olanzapine but this is when the dose is greater than 5 mg a day. And the weight gain summary is the amount of weight gain is significantly greater with Olanzapine. And the pooled estimates range from 1.8 to 3.9 kilos in difference in weight gain. And the proportions of patients with serious weight gain, and that is defined in all these settings as greater than or equal to a 7% increase in weight, was significantly greater in Olanzapine. And the number needed to harm range from 4 to 8. For the risk of diabetes evidence indicates that a higher risk of new onset diabetes with Olanzapine compared to Risperidone or to no treatment. The amount of increase in risk is not clear, however. And it is between one and 1.4 times the risk. There is extremely limited evidence on diabetic ketoacidosis. It does indicate an increase in the Olanzapine compared to Risperidone.

Now, moving on to Clozapine. Evidence for Clozapine versus Risperidone is a smaller body of evidence by far. There are zero effectiveness trials. There were ten head-to-head efficacy trials. And then there were a variety of other kinds of trials that we looked- or studies that we looked at, various types of outcomes.

So moving on to the next slide, this is looking at indirect comparisons for effectiveness outcomes. So 11 active-controlled trials, which are trials comparing Clozapine or Risperidone to an older drug that all reported effectiveness outcomes. And, again, here the only outcomes that we were able to compare were probably life outcomes. And there were only two of those that used the same measure. But they were good, long-duration trials. And they found no improvement compared to baseline with either of the drugs, and also compared to the typical antipsychotic [unclear] trials. And the other studies we were unable to make indirect comparisons with.

Moving on to the next slide, there were 10 head-to-head trials; six of these on treatment resistant patients, three on inpatients. There were no differences based on the symptom-measures, illness severity, response rates, things like that. There were also no differences in aggressive behavior in inpatients. There was one small inpatient study that did find that Risperidone resulted in lower- a bigger change in the BPRS scores for symptoms at three days compared to Clozapine, but no difference at four weeks. Similarly, this trial also found that Risperidone had greater withdrawal rates than Clozapine. Three other studies looking at withdrawal rates did not find a difference between the drugs.

Now looking at indirect evidence with observational studies- these are all before-after studies. And I simply listed a few things on this slide that were examples of the kinds of outcome measures that are reported. In the first bullet point there are- there were two trials, one of Clozapine- sorry, should be before-after study. Clozapine in teens with refractory disease and found reductions in need for medication for aggression behavior, and also reduction in seclusion episodes. And then similarly, Risperidone in adults also [unclear] found that reduction in episodes and time in seclusion, but no impact on restraint use. So similar types of outcomes

but not directly comparable. Then down below looking at- tend to look for social outcomes, we found new evidence for Clozapine. There was one study that found a significantly lower arrest rate with Clozapine among those who were exposed compared to those not exposed. But there is some caution in which results in that there was a significantly lower arrest rate among those exposed to Clozapine prior to those exposure. And [unclear] and they tried to control for it, but I think there's- really that is a concern with that study. Then the second thing is that there is no difference in employment or living situation after the patient's switched to Risperidone. Another before-after study.

Moving on to the next slide looking at adverse events, comparing Clozapine and Risperidone. Three of five studies found that Risperidone had a higher incidence or worsening of extrapyramidal symptoms compared to Clozapine. The dose of Risperidone of 6-12 mg per day in the studies that did show Risperidone to have a higher incidence. There's a single trial of Risperidone at 4 mg/day v Clozapine 400 mg/day that found no difference in use of anticholinergic medicines, where in that same trial the 8 mg dose per day of Risperidone did show an increased risk. Another point-prevalence study found a higher prevalence of EPS with Risperidone and the problem with this study is there is no control for confounding, including dose. Looking at the adverse event of hypersalivation, three trials found significantly higher rate with Clozapine. Similarly, somnolence, Clozapine again in three trials was found to have a higher incidence. Number needed to harm was nine. Looking at metabolic adverse events, one trial found serum leptin and triglycerides significantly elevated in the Clozapine group and not the Risperidone group. But observational studies, case-control studies did not find an increase in the risk of hyperlipidemia or glucose intolerance comparing Clozapine to Risperidone. So trial evidence conflicting with observational evidence there. Withdrawals due to adverse events, postural hypotension, also increase of constipation, there's no difference between drugs.

On the next slide, looking at weight gain, the proportion of patients with weight gain was not significantly different in four trials. The difference in actual weight based on two studies was not statistically significant. And the weighted mean difference was 1.28, too low [unclear]. Looking at the incidence of new onset diabetes, really the evidence is inadequate to make conclusions. There is 1 case-control study that found no associate with Clozapine or Risperidone. A head-to-head cohort study made no direct comparisons of the two drugs but just compared them to patients receiving no treatment. And another cohort study found Clozapine resulting in significantly increased risk compared to the other group of patients who were receiving no treatment. In the study we previously talked about with diabetic ketoacidosis there was an increased rate but the observation was not found to be statistically significantly different between the two.

So, summarizing the evidence on Clozapine versus Risperidone, one of the biggest problem with the trials is dose inequity. The dose of the Clozapine is low in many of the trials and in most trials the dose of Risperidone was higher than normal. The lack of differences found in trials and [unclear] efficacy could be due to these dose problems. And also a similar [unclear] findings of increased EPS with Risperidone does seem to be associated with higher doses. And increasing hypersalivation and

somnolence with Clozapine is found even with lower doses of Clozapine that are normally used. On metabolic adverse events I can put these findings, the evidence from the trials could be due to the dose problems just mentioned. Evidence from weight gain and diabetes is really inadequate to me [unclear] conclusions at this point in time.

Moving on to the comparison of Clozapine versus Olanzapine. This is a similar body of evidence. It's not- compared to the Olanzapine versus Risperidone evidence it's not nearly as much. But there is an effectiveness trial.

Moving on to the next slide, the effectiveness trial is a head-to-head trial of Clozapine and Olanzapine. It's called the InterSept trial. It's concerning Olanzapine and Clozapine in preventing suicide or suicidality in high risk patients. And the difference in the outcome measures at the end resulted in an NNT of 12. So there was a significant difference favoring Clozapine. In the update we found a post-hoc analysis of this trial that was looking at the use and the mean dose of concomittant psychotropic drugs such as antidepressants and found fewer and lower mean doses in the Clozapine group compared to the Olanzapine group.

Moving on to the next slide, the indirect comparisons. Again here we have very limited ability to make indirect comparisons. The quality of life. There were five studies looking at quality of life with Olanzapine. There was only one with Clozapine. Based on this one trial compared to the five there were no apparent differences. But other outcome measures were really not possible to make indirect comparisons. Resource utilization was reported in four settings. These are the before-after studies. Three studies showed a decreasing utilization after starting Clozapine and one showed a decrease after starting Olanzapine. But because they're measuring different [unclear] things, for instance [unclear] hospitalization versus number of episodes in hospitalization, they really aren't- you can't make direct comparisons across those studies.

Moving on to the efficacy trials on the next slide, there are nine head-to-head trials, two of those were in patient. No differences were found on the symptom measures, change in illness severity, response rates and early withdrawals. In the update we added an unusual study, a high dose study; 50 mg/day of Olanzapine compared to Clozapine 450 mg/day. And it was a small crossover trial. And the response rates overall were 10%, 10% of patients responded with Clozapine and none responded with the high dose Olanzapine. These were treatment resistant patients. The effect size for the change in BPRS with Clozapine were higher than the effect size with Olanzapine. A separate study there was no difference between the drugs found in aggressive behavior in inpatients.

On the next slide looking at the adverse events comparisons, for extrapyramidal symptoms reported in three trials there are no clear differences between drugs. Hypersalivation, somnolence and dizziness seen- for all of those outcomes Clozapine is found to have a significantly increased risk compared to Olanzapine. Numbers needed to harm are listed there. I separated out the InterSept trial because again, similar to CATIE, it's just much longer in duration. So do you really want to pool those together.

On the next slide looking at weight gain and metabolic adverse events, the difference in weight gain in four trials was not statistically significant. It was a very small actual difference between the drugs in terms of amount of weight gain. A small cohort study of inpatients found no difference in serum Leptin levels or in the amount of weight gain. Both drugs caused significant increases in inpatient study. Looking at metabolic adverse events, serum glucose two trials, looking at treatment resistant patients. In a 14 week inpatient study Clozapine caused significant increases at eight weeks, but the increase was not significant at 14 weeks. And Olanzapine the differences were significantly increased at both eight and 14. In a smaller eight week crossover study, this was the study of high dose Olanzapine, it changed from baseline was greater in Clozapine group compared to the Olanzapine group even with the higher dose of Olanzapine. However, remember that there was the case-controlled study that was in a variety of atypical antipsychotics and saw no difference in the risk of hyperlipidemia across the drugs.

So to summarize the evidence on the next slide, for Clozapine versus Olanzapine, in patients at high risk for suicide Clozapine is superior to Olanzapine in preventing suicide or episodes of suicidality. Differences in efficacy were not found. There were some trials with dose inequities, problems with lower- very low doses of Clozapine in this group, but not all of them. And findings were similar across the trials where the doses were low compared to the trials where the doses were not. Hypersalivation, somnolence, and dizziness were greater with Clozapine. No difference in weight gain was found. Evidence on the relative effects on lipids was really inadequate to make conclusions at this time.

Moving on to Quetiapine. A smaller body of evidence. One effective trial and a few efficacy trials. On the next slide this is summarizing the evidence for Quetiapine from the CATIE trial. And discontinuation for any cause. I have the drugs reversed there. It should be Olanzapine versus Quetiapine. So, again, Olanzapine is superior to Quetiapine with a risk difference of 18.1% and a NNT of 6. The time to discontinuation was also longer with Olanzapine compared to Quetiapine, 9.2 months versus 4.6 months. No differences with Quetiapine compared to Risperidone or Ziprasidone on this outcome measure. Discontinuation for lack of efficacy again with a significant difference favoring Olanzapine with a number needed to treat of 7. And time to discontinuation again was longer with Olanzapine. Duration of successful treatments, three months versus one month, the longer time duration of successful treatment with Olanzapine. Risperidone versus Quetiapine had very similar durations; one month versus one month but in the hazard ratio analysis the big difference was actually found to be statistically significant. With Quetiapine versus Ziprasidone there was no statistical difference between drugs. And there were no differences between Quetiapine and the other drugs in the PANSS or the CGI.

On the next slide looking at efficacy there were four trials, one of these was an inpatient, Quetiapine versus Risperidone, the QUEST trial. This was a trial that included patients with psychosis. So it included patients with other diagnosis other than schizophrenia. The primary outcome measure [unclear] is depression based on the HAM-D. The similar is reduction depression between Quetiapine and

Risperidone. And no differences were found in other measures. Quetiapine v Clozapine, Olanzapine, or Risperidone, no differences in the PANSS, the symptom based measure. Quetiapine versus Olanzapine or Risperidone in inpatient studies and no difference in sleep quality between drugs.

Adverse events. Looking at withdrawals due to adverse events and weight gain outcomes based on the CATIE trial. There is no statistical analysis conducted on these outcomes in CATIE. Data were not reported in a way that we could conduct the analysis. But it is reported that Olanzapine had the highest withdrawal rate due to adverse events. Quetiapine was [unclear] very similar and Ziprasidone had the lowest rate. And, again, there was no difference in the time to withdrawal due to adverse events among any of the drugs. Tolerability adverse events: Quetiapine versus Risperidone; somnolence, dizziness and dry mouth were all higher risk for Quetiapine compared to Risperidone with number needed to harm of 9, 19 and 14.

On the next slide looking at some metabolic outcomes, serum leptin, cholesterol and weight gain based on observational evidence, there were significant changes compared to baseline with Quetiapine. Compared to Quetiapine the changes were greater with Olanzapine and Clozapine but smaller with Risperidone. And for hyperlipidemia there was no difference, again, in that case-control study compared to Clozapine, Olanzapine or Risperidone. Looking at cholesterol measures, based on the CATIE trial again, Olanzapine had the highest impact on cholesterol followed by Quetiapine and then Risperidone and Ziprasidone were very similar. The Quetiapine was essentially equal to Olanzapine. Weight gain evidence was limited and conflicting for Quetiapine. In the CATIE trials the big difference was a number needed to harm was 7 with Olanzapine causing more- a higher number of patients who had weight gain. And also a larger actual weight gain. So a 3.8 kilos difference between [unclear] weight gain. Other evidence for Quetiapine was conflicting.

Looking at Ziprasidone the body of evidence is small. Ziprasidone was included in the CATIE trial, however. Moving on to the next slide, looking at the results for CATIE based on Ziprasidone and I think the most important point in this slide is the bottom point, which is that because Ziprasidone was added to the trial after it was approved, this drug was not on the market when the trial started the number of the patients, the sample sites for Ziprasidone is actually inadequate for [unclear] comparisons for most of these outcomes. The only outcome there that there were enough patients to [unclear] discontinuation for any cause, the primary outcome measures. Where Olanzapine versus Ziprasidone, again Olanzapine had a longer- or a lower rate of discontinuation with a NNT of 6. And a longer duration of treatment; 9.2 months versus 3.5. And the other comparisons were found to be not statistically significant. Discontinuation for lack of efficacy, again, Olanzapine was superior. Time to discontinuation was not significant between drugs. Duration of successful treatment three months versus one month. This difference was not statistically significantly. And no difference, again on the symptom-based measures. For many of these outcomes it is really unclear if the differences are truly [unclear] or if it's just a lack of power.

On the next slide we did in the update find two trials- efficacy trials. These were inpatients with acute exacerbations. They were six to eight weeks in duration. And the only difference; one was Ziprasidone with Olanzapine and the other was Ziprasidone with Risperidone. There were no significant differences on most of the outcome measures with the exception of withdrawal rates. Ziprasidone versus Olanzapine studies, where Ziprasidone had a higher withdrawal rate than Olanzapine.

On the next slide looking at adverse events comparisons for Ziprasidone the total number of adverse events were higher with Ziprasidone compared to Olanzapine. And weight gain was much smaller with Ziprasidone compared to Olanzapine. Cholesterol, LDL and triglyceride levels with Olanzapine had a higher impact, higher adverse impact than Ziprasidone. And these are data from CATIE trials. And the Ziprasidone actually improved the cholesterol levels. Ziprasidone versus Risperidone: EPS; there were more reports of or worse ratings for akathisia with Risperidone compared to Ziprasidone. Other EPS outcome measures there were no differences between drugs. And the Risperidone dose was high, it was 7 mg/day. Insomnia: Ziprasidone was greater than Risperidone. Prolactin: The Risperidone was the drug that caused increases there in both men and women, and the Ziprasidone did not. In CATIE the insomnia was again the highest in the Ziprasidone group compared to any of the other groups. The rate was 30% compared to the other groups, which are listed there. Weight gain, again, in CATIE the patients had an average of .73 kilos with Ziprasidone compared to 4.3 kilogram weight increase with Olanzapine. Cholesterol and triglycerides, as I mentioned above, improved with Ziprasidone and worsened with Olanzapine and Quetiapine.

Looking at the Aripiprazole data, there are no effectiveness trials. There are just two efficacy trials; one comparing the Aripiprazole to Olanzapine, and the other was comparing Aripiprazole to placebo and Risperidone. So in that trial there are actually no direct comparisons made between the drugs in the study publication. Looking across the symptom measures there are no apparent differences between the drugs. For Olanzapine versus Aripiprazole, again no differences based on symptom outcome. No difference in withdrawal rate in this trial, but the overall withdrawal rate in the trial was 72%, which is quite high, even for atypical antipsychotic trials, which do tend to have very high dropout rates. In this trial the withdrawal due to lack of efficacy is higher with Aripiprazole compared to Olanzapine.

On the next slide looking at adverse events, with weight gain in these two trials the percentage of patients with weight gain was 33% with Olanzapine versus 13% with Aripiprazole, which was significantly different. The amount of weight gain was also significantly higher with Olanzapine compared to Aripiprazole. Cholesterol and LDL there were no differences between drugs. But on triglycerides and HDL the adverse changes were that Olanzapine were much higher than Aripiprazole. Somnolence, Olanzapine [unclear] was higher than [unclear] significantly higher than Aripiprazole. No differences between the drugs in EPS outcomes. In Aripiprazole versus Risperidone EPS appears worse with Risperidone but one of the scores, the outcome measured scores, improved with Risperidone versus

placebo and Aripiprazole was not different to placebo on that measure. Looking at weight gain there was no difference between the drugs; the Aripiprazole and the Risperidone. And the somnolence, Aripiprazole at 20 mg/day had a lower rate than either the 30 mg/day dose or the Risperidone group.

On the next slide, looking at the evidence for the injectable formulations, Olanzapine IM versus Ziprasidone IM, there is no direct evidence. There are only two active controlled trials, both comparing the drugs the Haloperidol. But the outcome measures are different in the timing of measurements quite dissimilar. So can't really make comparisons there. Long-acting Risperidone Injectable compared to Oral Risperidone was- [unclear] difference in [unclear]. A noninferiority trial, 12 weeks long. In EPS there was no difference between groups. Although four patients in the IM group did report transient tardive dyskinesia. No indirect comparisons are possible for these particular [unclear].

Looking at the key question three of subgroups we found only evidence- very limited evidence of Olanzapine versus Risperidone, a post-hoc analysis from the Tran trial. It looked at the older subgroup of patients in a trial, which was the age group of 50-65, a very small number, only 39 patients compared to the overall study population. Olanzapine in the overall study population was not found to have statistically significant differences. In this [unclear] population [unclear] significant difference that was found was that Olanzapine is superior to Risperidone in reducing negative symptoms. New evidence in the update was done in two studies in older Japanese patients. These were studies assessing sleep quality. However, we don't have studies in younger populations to compare these outcomes to see if there's a difference based on age.

Moving quickly through the bipolar I disorder evidence; the body of evidence is very limited. No effectiveness trials. There are no head-to-head efficacy trials. So we're looking at indirect evidence only. And there is heterogeneity in the trials, so we actually [unclear].

On the next slide there is a table which nicely shows where all the studies are for the bipolar disorder. And you will see the Olanzapine has the largest number of trials and also the largest number of indications. [unclear].

On the next slide, to summarize this evidence, Olanzapine and Quetiapine are superior to placebo in the widest range of indications, but both were associated with [unclear] and weight gain. Risperidone was superior to placebo for acute monotherapy or combination therapy mixed/manic only. And associated with weight gain and EPS is unclear. The evidence is mixed on that. So Aripiprazole there were three trials. The drug was superior to placebo in acute and maintenance therapy of manic/mixed episodes. Insignificant weight gain and mixed evidence on EPS outcomes. Ziprasidone only one trial. Ziprasidone is superior to placebo in acute therapy of manic/mixed episodes and had insignificant effects on weight and EPS. Clozapine was found similar to Chlorpromazine in one trial of acute therapy of manic/mixed episodes.

Now looking at the patients with dementia, behavioral and psychological symptoms of dementia, limited evidence here as well. There is some direct evidence, however. Five Risperidone versus Olanzapine trials, but four of those were found to be poor quality. So the one trial that was left found no difference between the drugs or a placebo for the outcome measures. Three observational studies, no difference between Olanzapine and Risperidone was found in length of inpatient stay in one retrospective cohort study. Indirect evidence: Quetiapine versus Haloperidol was found in one study which was poor quality. And then there was Risperidone versus Haloperidol, which found Risperidone similar to Haloperidol in two trials but superior in another. Five placebo controlled trials, three of those were Olanzapine. Three fair quality trials of Olanzapine, which found a dose of 5-10 mg was superior to placebo but lower and higher doses were not superior. And another study, which [unclear] found it to be superior to placebo in inpatient and similar to Lorazepam in agitated patients. And Risperidone at low doses, 0.5-2 mg was superior to placebo in two trials. Now from this evidence there appears to be no difference in short term adverse events between drugs in this patient population.

Looking at children there are no head-to-head trials and no effectiveness trials and no studies on children with ADHD. Children with autism, Risperidone was found to be superior… [end side one of tape 2]

Marian McDonagh: [unclear] evidence was not helpful [unclear]. Children with disruptive behavior disorders; Risperidone was superior to placebo in three trials and one of these was with teens with comorbid subaverage intelligence. But it is one of the few trials with teens that we have in this report. Evidence on adverse events is limited. Weight gain was found in the trials. Short-term trials indicate more weight gain with Risperidone compared to placebo. Although the amount of weight gain is not reported in any of the [unclear] trials, weight gain is the most commonly reported adverse event in those trials.

Looking at serious harms overall, this evidence comes from a variety of different types of study. Looking at all cause mortality, originally we found only uncontrolled studies, studies that were descriptive [unclear], studies looking at rate of mortality among patients exposed to Clozapine, Quetiapine and Risperidone. In the update we found another study which was looking at the rate ratio of the two drugs, Clozapine and Risperidone, compared to older drugs, the typical antipsychotics. Both drugs were found to have an increased risk of mortality compared to the older drugs, but Risperidone had a more increased risk at 7.2. Along with this we also found the FDA warning, the results of the FDA meta-analysis looking at increased risk of mortality with the atypical antipsychotics in elderly patients with dementia. This is based on an analysis of 17 placebo-controlled trials and looking at Olanzapine, Aripiprazole, Risperidone and Quetiapine. So not including Clozapine or Ziprasidone. The rate of death was reported to have been 1.6 to 1.7 times that of placebo and most deaths were due to cardiac event. There's really no more evidence- information available about the evidence. Not all of the 17 placebo controlled trials have been published. So replicating these results or getting more information about the details is not really possible at this point in time.

Looking at cardiac arrest and ventricular arrhythmia, this comes from the same study that's reported above that reported rate ratios for Clozapine and Risperidone for mortality. This analysis found that the rate per 1,000 persons for cardiac arrest or ventricular arrhythmia was again increased when compared to typical antipsychotics [unclear] but the increase was greater for Risperidone.

On the next slide this is another- looking at another analysis that came out of the FDA. This is actually looking at cerebral vascular disease rate in placebo-controlled trials of Risperidone and Olanzapine. Risperidone versus placebo, four trials, two of those unpublished. The rates were four percent versus two percent. And with Olanzapine five trials, three unpublished. The rates were 1.3% versus 0.4%. So based on that the FDA and Health Canada have put out warnings for those- both of those drugs for increased risk of cerebral vascular events. And again, we don't have information on the unpublished trials, so we're trying to do a better analysis of this. It's really not possible until those trials are published. Increased risk of stroke, however, was not found in two retrospective cohort studies. One of Olanzapine and Risperidone and one of Olanzapine, Quetiapine or Risperidone. And let me just note there that Aripiprazole has also added- been asked to add a warning of increased risk of stroke.

Looking at other serious harms I think that your committee as well as others were very interested in some of the other serious harms. The evidence is very spotty. It's not complete and really it's not [unclear]. Neuroleptic malignant syndrome, one case reported out of almost 8,000 patients treated in the Mackay study reported neuroleptic malignant syndrome. Olanzapine, one case out of 25 in the open-uncontrolled study of Olanzapine. So here [unclear] evidence, especially not [unclear] for the drugs. Looking at seizures, the rates for Clozapine ranged from 1.3 to 10.8% in five uncontrolled studies. And no seizures were reported for other drugs in these types of studies. Looking at cardiomyopathy and cardiac arrhythmias, there was a [unclear] out of the World Health Organization database that did indicate an increased risk with Clozapine, a significant association. Associations were found with Olanzapine, Quetiapine, and Risperidone but they were non significant.

Tardive dyskinesia, the rate, I believe, of tardive dyskinesia with Clozapine is found to be 7% over 26 months in a single study. With Risperidone, two studies of general population, the rates were very low. In looking at a study of older patients, two studies, the rates were much higher, 2.6 to 5%. And an analysis of this evidence, along with other evidence from placebo-controlled trials, indicated that dose has a high association with the incidence of tardive dyskinesia in older patients. Agranulocytosis, again, the evidence as reported here is simply to be complete in report on the agranulocytosis risk for Clozapine.

Simply to summarize, the [unclear] of times of weight gain and diabetes that we've reported previously in the report, the Olanzapine has a higher risk of weight gain with a number needed to harm ranging from four to eight. And the amount of weight gain is greater with Olanzapine compared to Risperidone, 1.8 to 3.9 kilos greater weight gain. Ziprasidone appears not to cause weight gain on average. Clozapine does appear to cause weight gain but how similar it is to Olanzapine is

not yet clear. Comparison of weight gain with other atypical antipsychotics is much less clear and the evidence is still quite limited. Diabetes: The risk of harm is greater with Olanzapine compared to Risperidone. The risk of harm with Clozapine relative to the other drugs is really not clear. There is very limited evidence on Quetiapine. The observational studies that did include Quetiapine typically had very small numbers of patients exposed to Quetiapine. And there is no evidence on risk of diabetes for Aripiprazole or Ziprasidone.

So that is what I hope is not too long and too detailed of a summary of our report.

Dan Lessler: Marian, thanks, that was really an excellent review of a lot of detailed and fairly complicated information. So, really, we appreciate it. I think what we're going to do initially is open up the committee to ask questions of you and then what I think I'd like to do- we'll see how we go with time, 'cause, Dr. Farmer, what I was thinking is we could have the committee ask questions and actually, why don't we include you in that, if you wanted to address some questions to Marian. And then we'll actually maybe turn to you just to see if you have any additional or specific comments that you want to make. Does that sound okay to you?

Sharon Farmer: Sure, that's fine.

Dan Lessler: Okay. So, we'll begin just with questions from the committee for Marian on the presentation. Bob.

Bob Bray: This is Bob Bray. I have three questions actually. And we'll see if we want to interrupt this with somebody else's. But my first question was regarding the CATIE trial. It seems like there's a huge assumption that discontinuation means poor outcome. And I'm wondering if they looked at the outcomes associated with early discontinuation of the drugs as well. It doesn't seem like that was part of the study. Was that true?

Marian McDonagh: You know, I think I'm going to have to have you repeat part of that. I heard most of what you said, but the final part- I think what you're asking about is the decision of using that particular outcome as the primary outcome. But the part I didn't hear was what other outcomes [unclear] whether they looked at.

Bob Bray: Yeah. My interest is in those patients- you know, they have the discontinuation rate, and there's an assumption that because they discontinued early or at least they were looking at that as their primary outcome, that then we assume that the patient had a poor outcome, a poor clinical outcome because they weren't on the medication. So did they look at outcomes like hospitalizations, the rest, so on?

Marian McDonagh: No, they did not. No. No. They- and I do think that is probably the- there are a number of criticisms of this trial. But the- I think that is the biggest, the most valid one, is this the most important outcome measure. And you are correct, the other types of outcome measures that might be more interesting they're not reporting in the trials. At least not in the current publication. But based on their two or three publications early on about the method, it did not look like they were measuring those outcomes anyway.

Bob Bray: Okay. The second question I had was regarding the large odds ratio for diabetic ketoacidosis. And I'm wondering what the absolute risk was so that we could have a numbers needed to harm because my guess is that the numbers needed to harm may be quite large because diabetic ketoacidosis may have been a very rare complication. So do you have those figures?

Marian McDonagh: Oh, you know, that's a really good question. And I would have to go back and pull the paper to see if they give the actual numbers. If they simply give the odds ratio I could still calculate it [unclear], but I couldn't do it from over the phone.

Bob Bray: Okay.

Marian McDonagh: So not- I'm not exactly sure, but I would think you're right. I think that the other thing is that that is- it's one fairly small study. But I do think it should be taken with a grain of salt.

Bob Bray: Okay. The third question I had was Ziprasidone, as you mentioned, was a late addition to the trial and has lower numbers. In the adverse events that were discussed there wasn't any adverse events as far as cardiac disarrhythmias and I'm wondering if in that arm where they assign people to Ziprasidone did they do any filters by checking QTC levels beforehand. Or were they just randomly assigned to the Ziprasidone arm without that?

Marian McDonagh: Well, as far as I understand, [unclear] said, the two papers about method, and any publication I would assume that that was not done. That there was [unclear] screening ahead of time.

Bob Bray: Okay. Thank you.

Marian McDonagh: But it is- one of the problems is that it's such a complicated trial that there may be methods that were actually not included in all three of those publications. So I couldn't say for sure, but I don't think so.

Dan Lessler: Dr. Farmer, it looked like you might- you should feel welcome to jump in at any point, but it looks like you might have some comment about these specific questions.

Sharon Farmer: Is this turned on?

Dan Lessler: Yeah.

Sharon Farmer: Okay. Yeah, I agree. I'm not aware that they looked for QTC and changed which group people went into in the CATIE trial. I think the only thing that they used was whether or not the person had tardive dyskinesia. And since one of the arms of the study was into a typical antipsychotic, which wasn't discussed today, they didn't want to put people with tardive dyskinesia into that particular group.

Dan Lessler: Thank you. Other questions for Marian?

Angelo Ballasiotes: This is Angelo Ballasiotes. There's a big concern with regards to weight gain on these medications. There is some literature that has come from overseas, I think, with regards to using the Zyprexa [unclear] with regards to some control on that weight gain. Is there any studies in the future- are you aware of anything or any information with regards to possible [unclear] or the Risperdal M with the rapidly dissolved tablets?

Marian McDonagh: That's a great- really great question. And we did not find it. If it's out there [unclear] find it. And [unclear] also received quite a lot of public comments from most of the manufacturers of those products and [unclear] point it out to us in [unclear] comments. So it might be new- newer than that or I'm not sure. [unclear] included in the criteria, but it certainly is aware of it at this point.

Angelo Ballasiotes: Thank you.

Patti Varley: This is Patti Varley. You've alluded to this, but I just want to clarify in my own mind that as you've looked at a lot of the comparison studies, there seems to be a difference in what would be equivalencies of dosages between agents. Is that correct?

Marian McDonagh: Yes. It is correct. And I would be fairly [unclear] in saying that the problem is while some of the older studies of Risperidone [unclear] doses that would probably not be [unclear] right now. Those studies seem to not have as much of a problem as the Clozapine studies where the doses appear to be just very low.

Dan Lessler: Other questions for Marian at this point? Yeah.

Sharon Farmer: Yeah. Marian, this is Sharon Farmer and I just wanted to get your opinion on the issue of compliance with these medications. Was that typically addressed in these studies? Do they have ways of ensuring that the people were actually taking the medicine?

Marian McDonagh: [unclear] looked at outcomes measures such as resistance but not necessarily compliance as claiming direct outcome. So- but [unclear] method perspective. But I think that most of these trials [unclear] trials and [unclear] trials in particular didn't comment on [unclear] measuring whether the people were actually taking the drugs or not. I would say we don't have much to say on that, whether they were really and truly taking them or not, other than [unclear].

Sharon Farmer: Thank you.

Dan Lessler: Other questions or comment for Marian? Actually, Marian, I wanted to go back to that CATIE trial just to- the primary outcome measure of discontinuation rate. And I noticed, for example, that in some cases there were- the discontinuation rate was lower overall but the discontinuation rate for side effects was relatively higher. I think that was the case for Olanzapine.

Marian McDonagh: Right.

Dan Lessler: And I was just- more generally, was wondering if you could comment on just reasons for discontinuation. I mean, you know, were- why- if it wasn't for side effects, was it just because the patient wasn't responding? Is that- and what was the base- you know, the reason for discontinuation.

Marian McDonagh: Yeah. This is fairly important. And they did try to look at that to a certain extent by [unclear] the discontinuation due to lack of efficacy. They also [unclear] to patient decision. So just giving [unclear] decided by the patient that it isn't necessarily- couldn't [unclear] category of efficacy or adverse event. Between those three you should be able to add up to all of the discontinuations. But I think you're right. [unclear] efficacy, to go into that in a little more detail, is usually something that does determine between the provider and the patient that there is a lack of efficacy. So it would be based on let's say a certain- that they hadn't achieved a certain response rate. They would [unclear] a mutual decision between patient and provider. And [unclear] adverse event so it really- so it could be some lack of clarity there in terms of what the discontinuation is due to.

Dan Lessler: Thanks. Other comments or questions for Marian at this point? Dr. Farmer, I just wanted to give you another opportunity. I think where we're moving here with the more detailed discussion this afternoon and before we let Marian go, we wanted to see whether or not you had any other comments or questions with respect to her presentation at this point.

Sharon Farmer: Well, I was really glad to hear the presentation. I know she presented to the Mental Health Workgroup that is trying to support this committee and I wasn't able to hear that. And hearing the presentation and looking at the information again is really helpful so I was glad I was here for that. I have not come to any of these committee meetings, but my guess is is that this is one of the more complex groups of medications. Is that is that correct? And…

Dan Lessler: I think that's…

Sharon Farmer: Okay, good.

Dan Lessler: that's a safe assumption.

Sharon Farmer: Okay, good. And it seems to me that, in listening to the evidence, that there's no obvious winner in terms of either side effects or results taken as a whole. I thought it might be helpful to talk a little bit about how I think people make decisions in terms of selecting a medicine and this will just take a few minutes, but I think it might help highlight what I think some of this evidence shows. And I'm basing this just on talking with people and my own decision making, but also a report on some interviews with doctors that I read most recently in terms of how they select an antidepressant. And I think it's really similar. First of all, of course, you go with the diagnosis that you think the person has. And then next one would look at the unique features of that person's particular illness. So in the schizophrenia you might look for- well, in the case of this data suicidal ideation there seems to be in terms of positive outcome some evidence in support- some good evidence in

support of using Clozaril. But as a whole, there wasn't a whole lot of good differentiation between medicines in terms of aspects of schizophrenia. All righty. Okay. I'll keep going.

Secondly, you would look at co-occurring disorders. I'm not sure- there's a lot of co-occurring disorders with schizophrenia. I'm not sure that there's many that would actually help you chose your antipsychotic medicine. It's really more of an issue with depression and antidepressants. But then you get down to side effects and I think that is really where the need is in terms of this information, is that there is a fair amount of variation in terms of side effects. And I think that in choosing antipsychotics that's probably what people are looking at carefully; trying to match the side effects to issues like what's important to the patient, what side effects do they already have, are they already obese for example. But even that is really complicated, because when you think about weight gain, which is a side effect that people care about a lot, it is something that doesn't happen overnight. It is something that you can monitor and- so for a certain number of patients the risk really is not putting on 50 pounds and developing diabetes, the risk is are we going to have to change them to another medication fairly soon.

There are also side effects that tend to go away over time. I think sedation is one that tends to let up if a person takes the medication for a longer period of time. So, just to summarize, it seems to me that the harder the issue in terms of selecting medications in the area of side effects and then the side effects themselves have different features that kind of need to be matched to a particular patient.

Dan Lessler: I think that's very helpful in terms of developing a framework. Other questions or comments? Marian, I had one other question. Dr. Farmer had brought up side effects, very good point, and I just- in terms of cardiovascular adverse effects you had shown towards the end of your presentation the, I believe, observational studies that seemed like the take away point was that generally there's increased risk there. I was wondering whether there's any further delineation across these agents in terms of whether one or the other is associated with more cardiovascular risk.

Marian McDonagh: No. As a collection- the evidence that we have to date, some of it is [unclear] trials and some of it is observational as you said. And [unclear] risk for cerebral [unclear], [unclear] cardiac adverse events [unclear] little bit of [unclear]. It says cardiomyopathy seems to be the risk of [unclear]. But I would say the problem with that evidence is that it doesn't include all of the atypical antipsychotics that are on the market right now. [unclear]. [unclear] little bit of an [unclear] risk, but which one is worse, it's hard to tell at this point.

Dan Lessler: Okay. I actually was curious about Ziprasidone in particular just because of the- of what looked like a somewhat relatively salutary effect on intermediate outcome measures like lipids and such.

Marian McDonagh: Right. I see what you're saying. Unfortunately for Ziprasidone we don't have that kind of evidence yet, but [unclear] defined [unclear] benefits were any different from [unclear] drugs. [unclear] that kind of evidence was coming through [unclear] almost to observational studies [unclear] find that type of evidence there.

Dan Lessler: Thank you. Other questions or comments for Marian? Okay. Well, it's just about noontime. So, I think- Marian, thank you very much. It was really, again, an excellent presentation. A very complicated detailed information and we appreciate it. And I think we can let you go here. So, again, thank you and have a great day.

Marian McDonagh: Thank you. Always a pleasure.

Dan Lessler: And we will- yeah. Bye-bye. And we will adjourn until, then, 1:00 when we can re-adjourn at which point we will begin taking stakeholder input. Thank you. [end of recording]

Dan Lessler: It's going to be just another minute here because I think there's a number of other people who are signing up. So if we just take a minute and we're getting some more chairs for people to be able to get a seat. Okay. We're going to get started here. Again, picking up on our discussion of the atypical antipsychotics. And we're going to begin the afternoon with stakeholder input. There are a lot of people who would like to speak and so I really want to ask people to please limit your comments to three minutes and I will cut you off at the three minute mark so that we don't have to take away from some other individual's time. Also I would ask that people when they begin speaking, if you could just again identify yourself and let us know whether you're representing yourself or a particular organization and, as well, whether or not you're receiving any sponsorship for being here today and if so where that sponsorship is coming from. So, with that first I was gonna ask Judge Chow- Judge Chow is here, please, if you could start- thank you.

Judge Chow: There it goes. Thank you. I want to thank everybody for the opportunity to speak today. Jails were built to detain criminals, bad persons who willingly and willfully transgress the civil and social laws. The mentally ill are innocents guilty of nothing but laboring under disease. Jailing the mentally ill makes as much sense as jailing someone for contracting tuberculosis. I will give you the author of that quote at the end of my three minutes. And thank you very much. I am Judge Mark Chow, district court judge in King County. I have presided on the bench for over 16 years. I have presided on the second oldest Mental Health Court in the nation and in King County for over six years. I'm also the state chair for the Partners in Crisis. The Mental Health Court, and the reason why you have a judge here- you may not have had a judge ever speaking at this type of forum before, and I speak on behalf of the Administration of Justice and the Criminal Justice System, so that these other entities that you represent also understand that your systems affect the criminal justice system. In terms of the Mental Health Board there are three goals that the Mental Health and the Criminal Justice System has turned to with regards to mental health [unclear]; that's community safety, integration of system services and the decriminalization of the mentally ill. Community safety is one of the forefronts. You as you're reviewing things need to understand your decisions do affect community safety and the criminal justice system. Because at this point in time the criminal justice system is trying to address over 30%- anywhere from 25 to 30% of the mentally ill being housed in your local jails from your respective regions you come from in the state. And there are three things to make that successful, to keep that turnstile going and warehousing individuals with mental

illness; one, is they have treatment, two, is they have sufficient housing, and three is they have access to medication. If there is not access to medication then what you will see in your communities will still and continue to exist, which is the warehousing and the spinning of individuals in your local jails. This is apparent across the whole country. It is not necessarily just indicative of Washington. Without access to- without that leg of those three legs of the stool to be there, when someone gets out of jail, without those three legs then someone, a defendant, has a 75% chance of recidivism. So the access to medications are important. The lack of medications, you need to understand also, if they are not accessible, the mentally ill defendant is in jail without sufficient and correct access to medication, their mental illness is exacerbated by the environment in which they're in. They cost more. They cost more for your agency, they cost more for our communities. So the bottom line is whether or not there is access to medication that is going to be available to stop the warehousing of individuals and the criminalization of individuals in our jails. Two, whether or not having those access is culture confident. Whether or not the individuals of our diverse state have sufficient medication where there may be physiological lower metabolism rates on various medications. So access to all medications is very important.

I will try to sum up as quickly as I can because I know I only have three minutes.

Dan Lessler: Actually, your time is up. If you could sum up quickly, that would be great.

Judge Chow: If I could sum up. Without access to medication then the success of the criminal justice system that is trying to address will not be achieved. You will not have 80% of individuals that have those access to things not committing crimes a year after they're out of the criminal justice system. You will not have 115% decrease of assaultive behavior after they've graduated out of the criminal justice system and have those access to those three stools. Thank you very much.

Dan Lessler: Oh, one question, Judge Chow. The quote. Who is the author of the quote?

Judge Chow: Okay. Well, see, now you're making me go over. But that's okay. The last thing- let's not go back to the time of the quote, we're here now, we're here, we can address the thing. The quote was by Dorothy Dicks. Dorothy Dicks in 1842. An advocate for mental health and the decriminalization of the mentally ill. Thank you.

Dan Lessler: Thank you. Thank you, Judge Chow. Next is Peter Lukovich.

Peter Lukovich: Thank you, Mr. Sherman, and members of the committee. I'm here to deliver a message from your King County Sheriff. She is sorry that her schedule would not permit her to join you this afternoon and she wanted to share the following comments with the P&T committee members: She's been a sheriff's deputy for 27 years and the King County Sheriff for the past 16 months. During her career she has personally responded to calls for situations involving mentally ill offenders on a daily basis. Some of these individuals have simply not been on their medications. In these situations she points out there is always a risk of loss of life to the suspect and the responding deputy. It is a major problem in our jails throughout

Washington State also as they have become the treatment and housing facilities for the mentally ill in the new millennium. It just doesn't seem right. It is her understanding that in many cases, if not most, mentally ill offenders act out because they are off of or do not have access to the proper medications. We wind up taking them to jail, which she writes where the cycle begins and it just continues over and over and over again. As a result of the sheriff's work she writes, I strongly urge the pharmacy and therapeutics committee to recommend that all proper and necessary medications be made available at all times to doctors throughout the state to treat mentally ill- the mentally ill. Our doctors need to have access to the right medications to treat mentally ill patients. Lives of innocent citizens, patients, aid car workers and our police officers would be at risk otherwise when people act out due to their illness from lack of treatment from medications. If we used the best meds to treat these sick people then their chance of her deputies having to be in a position where the loss of life could result will be decreased. Finally, the life of a suspect and the life of law enforcement personnel should not be placed in jeopardy over what a medication costs or whether or not it is on a particular list. Please do not restrict access to the appropriate or necessary medications. Your decision could save lives. Thank you for your time and attention. Sincerely, Susan L. Rahr, King County Sheriff. If I may, Mr. Chairman, I'd like to make the letter a matter of the record. It's actually addressed to Mr. Thurman with passage to the members of the committee. So if I could pass that to him with your permission.

Dan Lessler: Yep.

Peter Lukovich: Thank you very much.

Dan Lessler: All right. Thank you. Next is- I apologize, I might not- Kim Lamyer?

Kim Lamyer: My name is Dr. Kim Lamyer and I am a neuroscience medical science liaison from Bristol-Myers Squibb. I would like to thank the committee for the opportunity to speak on behalf of Aripiprazole or Abilify. And more specifically my comments are going to focus in three areas. First I'm going to review the current indications for Aripiprazole. Secondly, I'm going to look at an additional effectiveness trial that was not included in the [unclear] report. And then I'll briefly review the mechanism of action of Aripiprazole. As noted in the package insert, Abilify is currently indicated for the treatment of schizophrenia, both acute and long-term maintenance treatment. It is indicated for the acute manic or mixed episodes associated with bipolar I disorder. And lastly, this is the four indication, it's for maintaining efficacy in bipolar I patients with recent manic or mixed episodes.

And given the time constraints, I'm really just going to focus on that most recent indication and provide you with a little bit more detail on that piece. Really this particular clinical registrational trial could be conceptualized in two phases; in the first phase with an open label stabilization phase. In here, bipolar I patients with recent manic or mixed episodes were first stabilized and maintained on open label Aripiprazole and they had to maintain that stability for at least six weeks. In the second phase of the trial was a double-blind [unclear] phase. The patients who achieved stability were then either maintained on their dose of Aripiprazole or randomized to a placebo and then watched for time to relapse. And the primary

outcomes to this study was time to combined aspect of relapses and Aripiprazole was superior to placebo on that primary outcome. This data was actually presented in poster format at the CIMP Congress in June 2004 [unclear].

To summarize, then, we have a wealth of data suggesting both efficacy in short-term and long-term treatment of schizophrenia and bipolar disorder. And then the piece in terms of a effectiveness trial that was not addressed in the [unclear] report, this was a trial of Aripiprazole in patients with schizophrenia or [unclear] affective disorder. Nearly 1600 patients were randomized to receive Aripiprazole or another antipsychotic medication. And the safety data only is included in the packets insert from this trial. However, it is available currently online in the Journal of Schizophrenia Research.

And finally, I'd like to touch on the unique mechanism of action of Aripiprazole. It is the first and only dopamine partial agonist. And this is distinct from every other drug in this class, which are all full antagonists for dopamine. But I'd like you to keep that in mind during this review as well. In light of the efficacy of safety data both provided by the OHSU report and the comments that I've made today, I'd like you to respectfully consider Aripiprazole for a drug for patients suffering from bipolar disorder and schizophrenia. And I'd be willing and happy to provide you with any of the references that I noted that were not included in the report.

Dan Lessler: Thank you. Appreciate it. Any questions? Okay. Next is Trina Clark from Eli Lilly.

Trina Clark: Good afternoon. My name is Trina Clark and I'm with the Outcomes Research Group at Eli Lilly and Company. Thank you for the opportunity to make some brief comments about Zyprexa. First, it's critical to realize that schizophrenia and bipolar disorder are lifelong illnesses that may potentially cause devastating consequences to patients, their families and communities. Clinicians must focus on maximizing the clinical effectiveness of chosen interventions. By clinical effectiveness I mean patients getting on therapy that works for them quickly, and maintaining that response as long as possible. Why is this an important outcome? We know that antipsychotic nonadherence is a significant cause of schizophrenia relapse. With each relapse patients can have more persistent symptoms, become less responsive to therapy and in effect become more treatment resistant and much more expensive to manage. When evaluating long-term clinical effectiveness you will see that there are measurable differences between agents in this class and that this is where the clinical and financial value of Zyprexa has been clearly demonstrated. One clinical effectiveness study that I'd like to highlight is the CATIE trial, an independent NIMH study. The primary outcome was timed to all cause discontinuation, which integrates both patients and clinicians evaluation of efficacy and safety. The Zyprexa dose range that was selected by the CATIE investigators was 7.5-30 mg/day with a resulting mean middle dose of 20.1 mg. The FDA approved dose range is from 5-20 mg.

In phase I of this study Zyprexa treated patients stayed on their therapy longer than all other atypical comparators. Zyprexa patients had a longer time- had a longer duration of successful treatment. Stayed on their medicine longer due to reasons of

efficacy and patient choice. And this latter is critical; patients simply chose to continue on their therapy longer on Zyprexa.

And phase II of this study, including both efficacy and tolerability arms of CATIE, Zyprexa treated patients continued to stay on their therapy longer compared to Geodon and Seroquel. For fair balance CATIE research also found that Zyprexa treated patients experienced a higher frequency of weight gain and elevations [unclear] values measuring lipid and glucose metabolism. However, it is hard to know if these changes were clinically significant since categorical analysis were not recorded with the exception of weight gain greater than 7%, which is a clinically significant measure. Additionally there were no significant differences between treatment groups in the addition of medications, like any diabetic and [unclear] medication.

Another compelling outcome of CATIE that was not mentioned in the Oregon presentation today and also was stated that this outcome was not included in CATIE, it was included in CATIE and that is hospitalizations. And calculated from the CATIE results, for every 1,000 patients treated with Zyprexa for one year instead of with one of the other agents, you could avoid between 160 and 370 hospitalizations. And it just indicate either are multiple studies that demonstrate Zyprexa's superior adherence and persistent, which were not mentioned in the Oregon report, as well as the body of evidence that has shown either lower relapse rate, higher study completion rate, and/or a higher percentage of patients maintaining response with Zyprexa.

Dan Lessler: Thank you.

Trina Clark: If I could I would like to address some questions that were posed by the committee members prior to lunch.

Dan Lessler: Actually, this is not a good time for that.

Trina Clark: Okay. But there was some incorrect information given about the CATIE trial, so I just wanted to correct that.

Dan Lessler: Not at this time.

Trina Clark: Okay. Thank you.

Dan Lessler: Thanks. Yeah. Next is Dr. Kareck-Walker from Pfizer. US Medical Pfizer.

Jill Kareck-Walker: Good afternoon. Hello? I'm Dr. Jill Kareck-Walker. I'm a clinical pharmacologist with US Medical at Pfizer. And I thank you for the opportunity to speak to you today about Ziprasidone or Geodon. It's well recognized by researchers and clinicians that there exists many differences amongst the atypical antipsychotics. Because of this Pfizer firmly believes it's very important to have open access to atypical antipsychotics. So like clinicians can provide the best care for their patients and match the appropriate medicines to individual patients. Geodon has both oral and IM formulations and it is efficacious in treating both positive and

negative symptoms of schizophrenia, acute exacerbation of symptoms with both schizophrenia and schizo affective disorder and prevention of mixed episodes with or without psychotic features associated with bipolar disorder. Geodon is the only agent that's been shown in placebo controlled trials to demonstrate efficacy as early as day two in bipolar disorder. In Zyprexa and Risperidone head-to-head randomized controlled-trials Geodon demonstrated equivalent efficacy and excelled in superior metabolic and tolerability profiles. This superiority in Geodon's metabolic profile has been acknowledged by consensus statement, by the American Psychiatric Association, the American Diabetes Association, published in the recent dual publication in the Journal of Clinical Psychiatry and Diabetes Care. Patients with schizophrenia and bipolar disorder are 2-3 times increased risk of diabetes. Thus it's important to have an agent not associated with this additional societal and cost burden. Unlike other atypical antipsychotic drugs, Geodon is not associated with the weight gain, hyperlipidemia and increased plasma glucose. Furthermore, Geodon has no increased signal of cardiovascular risk. And with the CATIE trial my previous points were confirmed as well as in phase II of the CATIE trial. Geodon is best in class regarding these metabolic adverse effects while maintaining efficacy. Geodon is an ideal switch agent because it has been shown to maintain in some patients improve the control of psychotic systems while improving metabolic and tolerability profiles.

In summary, Geodon has several therapeutic benefits and proven advantages over other agents in its class. Geodon provides powerful efficacy without compromising overall patient health, and broad and robust efficacy with proven tolerability, [unclear] positive patient outcomes. For these reasons Geodon should be one of the priority atypical antipsychotic agents maintained on the PDL. Thank you very much.

Dan Lessler: Thank you. Next is Eleanor Owenami. Mail in comments.

Male: That's who she represents.

Dan Lessler: Oh, represent- oh, I see. Representing- I'm sorry. So is Eleanor Owen here?

Male: She had to leave.

Dan Lessler: She had to leave. Okay. So then Dr. Mark Abrey?

Mark Abrey: Hey, everyone. Thanks for the opportunity to speak. My name's Mark Abrey. I'm a psychiatrist and medical director at Valley City's Counseling here in King County. That's my sole source of income. I have no industry sponsorship. I'm also here representing the Washington Community Mental Health Counsel, which represents the interests of community health clinics across the state. And I'm also sitting on the Mental Health Work Group along with Dick Mioshi and Sharon Farmer and a number of other dedicated folk. I'm here- the points I wanted to make today is on the Mental Health Work Group we're working very diligently on this very subject that you're talking about today. And that we're also in the process of reviewing and analyzing the Oregon Report. And we hope eventually to make recommendations to this committee once we've had a chance also to review that

data in detail. Jeff Thompson is helping us- helping to guide the process for us of breaking out the various risks, benefits, harms of the different antipsychotics so that we can analyze that in detail. We're looking at the strength of research for making choices within that class. Sharon already made the point earlier that the class of atypical antipsychotics is different from the previous drug classes reviewed in this last 12 months. The whole SSRI or second generation antidepressant discussion was very complicated. This morning's discussion was very complicated. And the antipsychotics- everyone was nodding their heads. So everyone knows that this discussion was even more complicated.

So I just wanted to make the point that the Mental Health Work Group was also working hard on this and I encourage you to wait for also our data to come back to you. It probably, I think, will be in the June meeting, before making any formal recommendations or motions regarding the subject.

Dan Lessler: Good. Thank you. Next is Melissa Johnson from AstraZeneca. Oh, wrong she- okay. Then Harrison Fisher.

Harrison Fisher: Hi, ladies and gentlemen, my name is Harrison Fisher. I'm representing NAMI Washington, NAMI [unclear] one mental health consumer living with schizophrenia. And as such I've been in recovery since 1998. Been around a lot of other consumers [unclear] 864 consumers that are in recovery there. And what goes on with my drug, which is [unclear], is that if I'm not on that drug or I'm put on Halodol or Navane, then within a week or so I'll want to commit suicide because the effects of the [unclear] from the drug is just too much. When I'm on Risperdal I'm able to go out in the community and make $95,000 in the stock market last year, do wonderful things for the community, [unclear] for the legislature and help the mentally ill get the services that they need to make. So I know that the committee is interested in buying some stock in our good friends in our express scripts with your bonus money, but that's not the way that mental health drug money should be spent. It should be spent on the mental health consumers not on enhancing the benefits for everyone else. So I have another friend that has schizophrenia that is on Abilify and [unclear]. And he needs to be on both of those drugs. In fact, on the [unclear] he has to be on the shot because he doesn't get enough of the blood levels taken care of with just being on the pill [unclear] all the time. When he's on both of those drugs he does wonderful. He's able to skateboard two or three hours a day, exercise with his family and if we had supported employment in this state, he'd be working. And if there was more support in this state for mental health consumers in employment, a lot more of us would be working.

And I have another friend that was on several combinations of drug with bipolar illness and thought he didn't need his Zyprexa, thought he could get by without it because he didn't like the weight gain. Well, a tragedy happened to him. First of all he got sick and then his wife overdosed on his Ziprasidone once he got the drug because they got- they had confusion in the household with the bottle. And she took the second highest amount of Ziprasidone ever recorded in history and survived, which was 864 mg. And recovered from that. Now they're both back working. But like Sharon pointed out, he's not working as well now on his last

hospitalization because it takes a year and a half to come back from that, or more, and when you do come back you don't come back quite as strong. So these drugs are important for all of us whether we need Ziprasidone, Abilify, Zyprexa, whatever it may be. Each of us is different and we need these drugs. It's based on gene types and sub gene types is some of the reason why this comes out. And also the drugs work to take 18 to 24 months to coat all the receptor sites in the brain. So it takes that long for the drugs to be effective for us. Now there are- you're weller at 12 months than you are at eight months, but you're not as you're going to be at 24 months. So that's my testimony. Any questions?

Dan Lessler: Thank you. Next is Miss Theresa Larson.

Theresa Larson: I hope I do this right. My name is Theresa Larson. I've been diagnosed with bipolar I disorder with psychotic features. I was quite offended by being quickly through presentation. We need to be seen and heard on these things. I need Wellbutrin and Abilify to survive. If you take them away I won't be able to function. I was diagnosed in May of 2002 with the bipolar disorder after going completely mad and I was very fortunate not to have police involvement, but it was very narrow escape. And I was in the hospital and the medications they gave me in the hospital were so bad that all I did was sleep and eat. And I was very fortunate that the psychiatrist that I was sent to was being used as a test case for Abilify and I was able to get Abilify in the fall of 2002. And he said it was safe, that it was recently been FDA approved for bipolar people because it had been FDA approved for schizophrenics. And so I took it and I began to be all right. I could function. I could stay awake. I could go to support groups [unclear]. I came in on the [unclear] carpool. I'm not getting any money from [unclear] and I'm not getting any money from my psychiatrist to come here and tell you that it's a good thing. He said his patient's are doing fine on Abilify and there's no side effects. I'm- my weight has gone neutral and I'm dropping weight now. And I have a friend who is having the same situation happen to her. Abilify is working very well and she is now looking for a job. Thank you.

Dan Lessler: Thank you. Mr. Alex Paine.

Alex Paine: Hello, my name is Alex Paine and I'm a person who suffers from schizophrenia. I have been on Ziprasidone for a year and it has given me hope. I have my sanity back and can function and life is easier for not only me but for people around me such as society as a whole, my friends and family. I would like to explain to you how sick I was before I had Geodon. I had a scheme in my mind going that the mafia was after me. And I thought that they were trying to initiate me into their gang. So I thought I had to murder someone to join the mafia. And that's what I was thinking. That's how sick I was. So, basically, before I had my Geodon, I was ready to blow someone's head off with a firearm. After I had my Geodon, I recovered. Now I don't want to shoot people in the face anymore. I'm not a violent person anymore. Everyone should have the right to sanity. I'm 20 years old. Ziprasidone has given me my hope and my life back. Why change something that works. I have my whole beautiful life ahead of me with Ziprasidone. Nothing else. And quite frankly the slide show this morning meant nothing to me because in my opinion a study like this needs to be at least two to four years long. Basically

what this [unclear] says to me is that low income people don't have the right to be sane. And I think that's wrong. I'm 20 years old. I've been through hell and back. And I don't need to do that again with my sickness. No one needs to do that again. Nobody needs to go through the hell of getting sick and adjust to the meds again because that takes months out of their lives. So basically I want you all to ask yourself, Should I have my Geodon and be a normal part of society and go to college or should I be sick with a gun pointed at peoples neighborhoods and shooting people in the face.

Dan Lessler: Okay. Next is Miss Glenna Robertson.

Glenna Robertson: Can you hear me? My name is Glenna Robertson and I'm a friend of Alex and I'm very proud of you, Alex. I am with [unclear] in Tacoma, Washington. And I have lived with my daughter who has schizophrenia. And it is very painful. Very painful not to be able to help her because I don't have the money. So I'm very grateful to the state that it has given Olanzapine to Cynthia and that has helped her a lot. And I feared, you know, because of the lack of money and the lack of case managers, you know, she would go to waste. Right now she is in Western State because we didn't have the means to help her. And I'm getting emotional. What I want to say is so much so much that I cannot do it at once. But, I think- I am a foreigner as you can see, but I've been here longer than many of you. But still- but I can see the value of choice. And in this day choice is what is best for the patient. Choice [unclear], choice. Do not put us in a box. We need to have choice. Or you know what happens when you don't have a choice. Thank you very much.

Dan Lessler: Thank you. Dr. Susan Cabberly. Did sh- okay. Dr. Cabberly? Brendon Williams? Burroughs Lloyd?

Lloyd Burroughs: Good afternoon. My name is Lloyd A. Burroughs and I am the Washington State Commander of the National Association for Black Veterans, Incorporated, or NABVETS. Over the last three to four years NABVETS has diligently advocated on health disparity issues for veterans in communities of color including access to much needed medication. Genetic research in the past few decades has uncovered significant difference among racial or ethnic groups in metabolism, clinical effectiveness and side effect profiles of therapeutically important drugs including atypical antipsychotics. It is now well documented if substantial disparity exists and quantity and quality of medical care received by minority Americans, especially those of African, Asian, Hispanic heritage. Pharmacogenic research in the past few decades has uncovered significant differences among population groups in the metabolism clinical effectiveness and side effect profiles of many clinically important drugs. In addition, differences in how various populations respond to medication underscores the need for an individualized approach to pharmaceutical therapy. Historically, the special needs and responses to the pharmaceutical treatment of these groups have been undervalued or ignored. It is in this context that we believe that evidence support ensuring access to all medications that three schizophrenia and bipolar disorder. Physicians must be able to provide individualized treatment to each patient prescribed drug therapy that takes into account racial or ethnic origins and sub cultural influences.

I am a combat infantry man who has served two combat tours. I have seen the impact of mentally illness on the battlefield and the havoc it causes at home. It has left many totally devastated due to a lack of treatment. Often many end up homeless or in institutions or in jail. Please ensure that our veterans in the community of color are able to have access to all atypical antipsychotic medications. One of the things I will say is that when I went on my combat tours it was never a question of when you run out of money we're bringing you home. I was there until the battle was won or it was time to return back to my home. And I want the veterans that we see today, especially those veterans in Washington State who are National Guardsman and our Reserves, to be able to get the medications that they need regardless of expense. Because when they went to combat nobody said you can return home as soon as we run out of money. So I thank you very much, and I've left some handouts. And in the handouts there is an enclosure written by Dr. Valentine J. Burroughs talking about disparities in the health care. Any questions, please.

Dan Lessler: Thank you.

Lloyd Burroughs: Thank you.

Dan Lessler: Next is Dr. Sam Rapport.

Sam Rapport: My name is Sam Rapport. I'm a psychiatrist practicing in a fairly small rural community in Eastern Washington. And I'd like to take a minute to describe our patient load because it's going to be relevant to other comments I'd like to make. For the last four years I've been supervising what we call our medication clinic. This consists primarily of very chronically ill and handicapped individuals with mental illnesses. Most of whom have been on every medication you can imagine, including all these six atypicals. And we're only sorry there aren't a few more to choose from. So, basically my appeal today is not to restrict the choices because there are many people in this category and I might say in regard to some of the sheriff's comments that we consider the county jail our annex and we have a number of patients who find their way into the jail, but we're available to the nurses there to prescribe medication, to supervise medication, even supply it when they don't have it available. But the patients in our clinic, when they come to us have been on two, three, often more medications of various types and either they haven't responded to it or they had disabling side effects, or they did respond and they the response kind of pooped out, which happens with a number of these drugs. So we had to make a choice of a different drug for them. And I think for us to have to pick from a small group, we consider a small group the six, because we get patients from many different sources. From discharge from the state hospital, Eastern State Hospital, from the jail, from various practitioners in our two county area. And these are people who have really nowhere else to go. It's a large clinic. We have 1,000-1200 patients at any one time and they're all very much in need of individualized treatment and medication. And those who are doing well when they come to us, we provide ongoing monitoring of their mental status and prescribe medications, and those that aren't we try to find something that will work better for them. And very often a number of the atypicals that have been discussed and talked about here have already been tried and either didn't work or had disabling

side effects. So it's very helpful to have other choices. That's my major concern is that our choices not be restricted for this category of patient because otherwise they're very difficult to treat and maintain in the community. Thank you.

Dan Lessler: Thank you. Alan Woo?

Alan Woo: Good afternoon. My name- can you hear- good afternoon, my name is Alan Woo and I am with the Medical Affairs Department. We are with Ortho-McNeil [unclear] Pharmaceutical. I would like to spend a few minutes addressing the issue of partial compliance in patients who have schizophrenia and the use of [unclear], the only long-acting atypical antipsychotics currently available to patients. In both topics we see limited attention in the OHSU review. Studies have shown that about 50% of all patients with schizophrenia become partially compliant with their medication within the first year of treatment. And 75% by the end of the second year. Studies have also shown that partial compliance began [unclear] occurring in 15-25% of outpatients after only 7-10 days of post discharge day. Unknown partial compliance complicates the clinician's ability to determine optimal treatment regimen resulting in increased breakthrough symptoms, hospitalization and [unclear] pharmacy. Risperdal CONSTA is approved for schizophrenia and is key to addressing the issue of partial compliance. Risperdal CONSTA is administered intramuscularly every two weeks, and because Risperdal CONSTA is a long-acting formula, patients compliance with their medication is known and more likely to be ensured. There have been several studies that have shown some great results. In a one year double blind trial Risperdal CONSTA patients experienced psychiatric hospitalization at 6% in a 50 mg group, and 10% in a 25 mg group. Much lower than what we see with oral medication. Especially with patients who are not compliant with their medication.

In a pre-post international study, patients treated with Risperdal CONSTA on an average of 3.5 years was shown to reduce number of hospitalization by 50%. And if patients were hospitalized, the mean duration of inpatient stay was reduced to 64%. Efficacy and safety of Risperdal CONSTA has also been demonstrated in a 12-week double blind randomized study and a one year open [unclear] trial in stable patients. All studies cited could be provided to you at your request. In conclusion, Risperdal CONSTA is a long-acting atypical antipsychotic that provides unique therapeutic solution to address- addressing partial compliance, hospitalization and relapse in patients with schizophrenia. It should be considered for PDL list and patient access. Thank you.

Dan Lessler: Thank you. Dr. Devarcy?

Dr. Devarcy: Good afternoon. My name is Dr. [unclear] Devarcy and I'm a regional scientific manager for AstraZeneca. I appreciate having the opportunity to speak with you today about Seroquel or Quetiapine. On behalf of AstraZeneca, [unclear] our full support of maintaining open access for the [unclear] agents. Seroquel is indicated for the treatment of acute manic episodes associated with bipolar I disorder at either monotherapy or adjunct therapy to the [unclear] and for the treatment of schizophrenia. Since its launch in 1997 Seroquel has had more than 13 million patient exposure worldwide. The principal cause of noncompliance with

antipsychotic medication is related to their side effects. Seroquel is the only atypical that has demonstrated placebo level extrapyramidal symptoms including akathisia, across the entire dosage range. [unclear] trials for both schizophrenia and bipolar mania. Seroquel has also demonstrated a placebo level stable prolactin profile and a stable [unclear] profile with no discontinuation [unclear] in [unclear] trials. In both schizophrenia and bipolar mania trials rates of discontinuation due to adverse events were similar between Quetiapine and placebo. The most commonly observed adverse events due to the use of Seroquel include somnolence, dizziness, dry mouth, constipation and dyspepsia. In September 2005 the New England Journal of Medicine published the stage I results of the CATIE schizophrenia trials. This was a study of the complex multi phase study [unclear] a body of evidence evaluating antipsychotic medications for the treatment of schizophrenia. This study points the importance of balancing the risks and benefits to patients in choosing an antipsychotic. For the primary outcome measure a lot of [unclear] patients had a longer time…(end of tape)

Dr. Devarcy: …150% of the maximum FDA approved dose. All the study medications other than Olanzapine were given their FDA approved ranges and performed comparably. The [unclear] dose of Olanzapine exceeded the maximum FDA approved dosage. The average daily dose of Seroquel was 543 mg. Comparison of atypicals in first episode psychosis or [unclear] is another recently conducted effectiveness study comparing Quetiapine, Olanzapine and Risperidone in the treatment of first episode psychosis. It is a study design similar to phase I of CATIE [unclear]. The CAFÉ results show comparable effectiveness as measured by all cause treatment discontinuation for Seroquel, Olanzapine and Risperidone. All medications for dose within the FDA approved dosing range in this study. Hallowell conducted a patient preferences study in which patients received Seroquel for at least six months. 97% of patients preferred Seroquel to previous treatment. In summary, AstraZeneca is in full support of maintaining open access for the class of atypical antipsychotic agents. Within the drug class Seroquel has demonstrated a balance of efficacy, safety and tolerability and is a safe and effective atypical antipsychotic. I thank you for your time.

Dan Lessler: Thank you. Next is Dr. Penny Tanner.

Penny Tanner: Hello. My name is Dr. Penny Tanner. I'm a psychiatric nurse practitioner. I'm board certified in three different areas of psychiatric practice and I have a private practice in Lake Wood and I do have a percentage of DSHS patients that I serve. I was going to review study data with you, but I think you've been bombarded with that enough. So I'm going to give you a brief idea of what I've learned about the differences between the typicals and the atypical agents in my own clinical experience. As I may have told you, I'm not sure, I've had about 25 years in the field so I had a lot of time to see what has come and gone. As a younger practitioner when I could see the devastating effects of the long-term use of the typicals, I said to myself, I cannot use these. When I came here and became a nurse practitioner at that time atypicals were available. It was a God send. My job is to rescue, restore and protect that brain. And in my experience and from what I've learned, the typicals do not allow the degree of cognitive improvement that we receive from the atypical antipsychotics. Cognition is paramount. Executive

function is paramount. I have actually seen in transition, from typicals to atypicals, the lights go on. Now I don't have a clinical term for that, but I think you've experienced from some of the patients' testimony that these have made a difference in their life. In my practice I have a total of three people on a typical antipsychotic. I almost refuse to use them. That's how I feel about them. I treat children. They also have schizophrenia and bipolar disorder. How can I assign a typical agent to that child knowing that I'm not providing the best cognitive protection for a lifetime that I can. Thank you so much for having me and I will answer questions if you have them.

Dan Lessler: Thank you for your comment. Next is Sylvia Magone. Hope I pronounced that correctly.

Sylvia Delagdone: My name is Syl Delagdone. I'm a psychiatric nurse practitioner. I have been a psychiatric nurse for over 28 years. And I won't be talking- I came here on my own will to support the open access to atypical medication. I remember the first time I started doing psychiatric nursing. It was acceptable at that time to put a patient into an insulin shock and then to give the patient lots of sugar to wake them up, hoping that when they wake up their brain would be back to normal. We all knew back then it didn't work, but our only alternative at that time was using the [unclear] medication. And it was so easy to spot those patients when- you know, if I'm shopping at the- you know, by the Safeway store because you know they would be grimacing their face or walking around trembling their hands. Or maybe doing the [unclear] motioning their hands. And sometimes they have the funny walk that we call the [unclear] shuffle. But patients became out of control, you could give them [unclear] Thorazine, Halodol and sure they are as stiff as a board. And then when they wake up they are very docile, but then again they; are still as stiff as a board. So ten years into my practice atypical medications were made available and that made a whole lot of difference for us. We were able to select what kind of medications we can give to the patient based on what they can tolerate, the side effects, their sex, their gender, their ethnicity. It was so nice to see these patients in groups and get out of the state hospital and be able to be productive citizens of our community.

Let's not go back to the time when we had to make them be stiff as a board again in order to control their behavior. We have aggressive patients now that we can control with [unclear], but we don't have to make them like that. You know, they're able to make choices now. They're able to make the right choices and be productive in out society. So, please, let's keep the open access going for medications.

Dan Lessler: Thank you. Next is Sue McCurty.

Sue McCurty: I'm Sue McCurty and I came over from Wenatchee representing the Promise Club. Promise Club is a consumer based agency. I'm on staff there and we focus on returning as many of our members to a recovered life style, working, educating, just living a comfortable life. They're vulnerable people and change is terribly upsetting. Particularly drug changes. Every time an agency, an insurance company, the federal government does not pay or removes a medication from a list,

we see crisis on many different levels. It may be simply bad depression or major depression or whatever, all the way to hospitalization. Our members feel like- some of the things that are said, Well, you can pay $12,000 for my medication to keep me sane, to keep me employed, or you can pay $32,000 for me to stay in the hospital, or support me in jail. And I would urge all of you to listen strongly to the testimony that has been here today that is promoting. Please, please, do not remove these medications. It isn't a case where one medication fits all. It's very individual basis. And it affects people's lives. As much as if you removed a antibiotic or something that saved their physical life, these are just as important. Thank you.

Dan Lessler: Thank you. So next- I just wanted to recognize some members of the legislature who are here with limited time. So I was gonna ask for their input currently. And first is Senator Parlett from Wenatchee.

Linda Parlett: Thank you very much. I am Senator Linda Evans Parlett representing the 12th legislative district which includes Chelan and Douglas County, part of Grant and part of Okanogan. I also am the co-chair of the Mental Health Task Force, which was formed two years ago. I co-chair that with Representative Eileen Cody. And I have served in the legislature for ten years; four in the house, six in the senate, and the Health Care Committee is one of those committees that I've sat on for the full ten years. I am here actually, however, as a registered pharmacist. And I do continue to practice at least one day a week during the interim at the Wenatchee Clinic pharmacy. And so I'm speaking to you as someone who just needs a process when I fill a prescription for somebody who's in need. I'm very clued in to the importance of continuity when you are helping people who have a mental illness disease. So I would just ask that as you make your evaluations- and I understand the difficulty when you are looking from the state side, an ability to be responsible in how we spend our money on these drugs. But also on the consumer's side, trying to get the right medication for a person, whether you start out the right time with it the first time or you don't. But some process, so whoever that registered pharmacist is who gets a prescription, some ability for us to know that we can count on a process that will work. And I'll leave that up to you for those details. But I think it's important to think of that whole sequence as you discuss this issue. Thanks very much.

Dan Lessler: Thank you. And Representative Alexander from Olympia.

Gary Alexander: Thank you very much. Pleasure to be here. And thank you for conducting this- these public discussions. I am representative Gary Alexander from the 20th district and that includes parts of Thurston County and all of Lewis County. Like Linda I came in here ten years ago, I'm starting my 5th term. I've been on the Health Care Committee for eight years, about ten as well I'm a ranking minority member on the Preparations. And this issue is both an issue of health care and a fiscal issue. Just thought a little bit of background. The mental health population is one that I've worked in the industry as well. The vulnerability of this population is one that I think is the most extreme from our standpoint of responsibility as legislatures. And that's why one of the first bills that I sponsored in the legislation was to provide special appropriation to review atypical psychotic medications in a pilot type setting to recognize what are the side effects and outcomes that occur of our

consumers who have access to or non access to antipsychotic medications. And unfortunately that pilot was not successfully concluded. So I'm hoping that you will take a very serious look at this because I've also sponsored legislation to carve out from our Preferred Drug List mental health as a drug along with diabetes and HIV AIDS. And I really believe are the most sensitive populations to changing medications from a cost perspective. And I know you're not talking about dollars and sense right now, but that is an important issue at some point in time. And currently the projective savings we've been expecting to realize from going to non brand names hasn't materialized. And I hope that we look at that in the future. But let me just say please expand your study base out there to ensure you've got a good basis for understanding what the impacts are on this population if we require them to go to a preferred formulary drug list and take them off of the medications that they are currently on because to me there's no cost benefit analysis that goes with that situation. So I'll be following your reviews very much. And please listen to the audience out here today, because all the consumers they will tell you the stories and we're listening to legislatures. Thank you very much.

Dan Lessler: Thank you. And next is Brendon Williams from the 22nd District State Representative.

Brendon Williams: Thank you very much for having me here today. I am Brendon Williams the State Representative from the 22nd District, which is the cities of Lacey, Olympia and Tumwater and then parts of North Thurston County. I have been following the work of this group. It's of special interest to me. I'm a member of the House Criminal Justice and Corrections Committee. And I would like to echo some of the concerns expressed by my colleague, Representative Alexander. I do have concerns about anything that might short change those with mental health diagnoses. This is a concern that I think become, if anything, more acute to me in my work on the House Criminal Justice and Corrections Committee and seeing a lot of persons incarcerated with mental health diagnoses and not really feeling that our state prison system is an appropriate place for mental health intervention, which I would just as soon see occur short of incarcerating people. I was recently touring the state penitentiary in Walla Walla and that really just brought it home to me, I think. And then just some of my own work as a graduate student in criminal justice- it's a resident theme in the work that we do as a Criminal Justice and Corrections Committee. Earlier today the chair of that committee, Al O'Brien was here. He had to leave for another engagement. But I think, as did Representative Alexander, what I would say is that your work is of considerable interest to those of us in the legislature. I do have some concerns looking at your earlier slide show presentation and just the statistical sampling. Because, after all, what we are about here is achieving evidence based medicine. And when I see 306 studies included overall but 20 fair to good quality systematic reviews, from my own recollection of graduate level statistics course in pursuing a masters degree, that is somewhat lacking. And so I really would also encourage you to listen to the testimony of those who are here in this room and applaud you for what I know is very difficult work, from which I'm sure you will derive the right conclusions. Thank you.

Dan Lessler: Thank you. Next is Pat Forney.

Pat Forney: I just- first off, I'm scared to death up here. And- but I think this is a good cause because I am here, Pat Forney, to tell you my side of the story of if these medications go off. I have had to change my- I was on Zyprexa and my insurance lapsed so I had to change to another one because I could not afford it because it was $1,025 a month. After doing that I went into a crisis and they had to put me in the hospital and I was there for 28 days, trying to get back onto another type of medication without hurting myself as when I was at the bad state I was wanting to do suicide. And so when we took it off it was like taking my life more or less, hanging me out to dry and just saying, well, there's nothing we can do. I was in the hospital and I did some figuring the last couple of days and Sue said something I was going to say, which was I- for a year on Zyprexa would be $12,000. Little over 12,000. 13- around there. And I was put in the hospital and I got the bill, or the notice of billing from them that I was charged $35,000. The state picked that up. So in my logic, you do the math. That's three times the math of what- if you guys helped pay for these drugs that you wouldn't have to pay if you kept 'em on. And we wouldn't have to change and worry about doing- not living here any longer or being a part of society. Thank you very much.

Dan Lessler: Thank you. Christine Gill.

Christine Gill: My name is Christine Gill. I'm a member of the Promise Club in Wenatchee, Washington. And what I wanted to say- and Sue's already said this, but it needs to be said again. One medication doesn't fit all. And I'm here today because I am a stakeholder. I noticed that on the paper. I have bipolar disorder and I've proven that if choices are limited more of us will need hospitalization or end up in jail. The cost of these choices costs much more than taking away certain drugs. I've had a roller coaster ride with medication. Because of losing insurance and getting insurance, I would always have to change doctors, and it seemed like every time I changed the doctor they would change my medication because I had- had to put their own stamp of approval on it, I guess. But whether or not the ones I had been taking, even if it had been working and I was feeling good, they would change it. And at one point I was doing great on Geodon and a new doctor decided he would switch drugs. Within two weeks I was suicidal and ended up in the hospital for a week. And I'm sure that costs thousands of dollars for the state. I'm back on Geodon and my way to recovery. We need the choices because we all respond differently. Thank you.

Dan Lessler: Thank you. Charles Albertson.

Charles Albertson: I'm Charles and I'm representing Rainbow Center. And I'm the chair of the North Sound Mental Health Administration. Mostly I'm representing myself. I'm a mental health consumer. I take Stelazine, I take Risperdal, I take Geodon, I take Depakote, and I take Topamax. A lot of stuff. Mostly I take Stelazine because that's the stuff that works the best for me. But I need those other things too. I need the Geodon because of the manic part of my illness. I need the Topamax because the Depakote makes me gain so much weight. And I need the Depakote because of the manic part of the illness. I need the Risperdal because I need help to control my sexual urges, because without that I become a sexual deviant and become a threat to society and have hurt my family because of that. And not very proud of

that. So it's important to have the Risperdal. It's important to have the Geodon. It's important to have all those things. And the Stelazine is making me shake. I would just as soon do without the Stelazine and find something that would replace it and maybe someday I will.

Dan Lessler: Thank you. Russ Sabienza.

Russ Sabienza: Good afternoon. My name's Russ Sabienza. I'm from Bellingham and I work as a peer advocate for Rainbow Center and also I am a consumer. I'm on Seroquel and for several years I was on Paxil but it was switched to Paroxetine. I haven't had any- too many problems personally, except for the weight gain and for sleeplessness. But as a counselor at Rainbow Center- well, as a peer advocate at Rainbow Center, we have over 2,000 people in our group and we serve 60-90 people a day. And these people have gone through a tremendous amount of crisis because they're off medications that they need. And as was mentioned earlier, we seem to have, I think all of us I guess have this idea that well, if it works for me it will work for you. But I realize now that it's not like that. Mental illness is as individual as a fingerprint. Everyone's biology will respond to different medications. We're asking that you don't take the meds that are needed. Especially the atypical medications; the Wellbutrins and the Zyprexas and the Geodons. All these medications are very important for those who are undergoing the struggles of mental illness. Are there any questions so far from anyone here? But I do want to thank you for taking part of your time to listen to us, and hopefully we will have this situation solved. But the bottom line is we need atypical meds. That's the bottom line. Thank you very much.

Dan Lessler: Thank you. Marcia Benoit.

Marcia Benoit: I'm Marcia Benoit from the Rainbow Center. It's a drop in center for people with mental illness. I'm being sponsored by NISMA. I have a schizo affective disorder and I take Geodon, which is prescribed by my psychiatrist. I need this medication to function. Thank you.

Dan Lessler: Thank you. Dick Mioshi.

Dick Mioshi: Dick Mioshi, Harborview Medical Center, University of Washington, and actually member- semi-member of the Mental Health Work Group. As we've heard from both CATIE and OHSU, there are no clear winners in this group. There are also no clear losers. So the Mental Health Work Group has this unenviable job of trying to figure out what to do with everything. So we're looking at off label uses, looking at ages; what's too young, what's too old, what- dosing, whether high dose- and whether we're actually going to be able to look at what low dose is with all the new data on augmentation for depression is going to be really tough. The-one of the more contentious things is going to be combinations. You've heard multiple people say that they're on combinations of atypicals. We're going to try to do that in a thoughtful way that will support the people who are on the combinations and try to figure out how to get them to have the best outcome. Then we will work on recommendations to the DUR and then finally, but probably not this- we're going

to have to work on the education and the communication to the providers. We're going to have to implement all this. Thank you.

Dan Lessler: Thanks. All right. Are there any questions for Dick regarding the Mental Health Work Group? And finally, Eileen Propoor?

Eileen Propoor: Hello. I'm Eileen Propoor and I'm a psychiatric nurse practitioner. I'm coming here today not as a psychiatric nurse practitioner but as a mother. In 1997 my son developed schizophrenia and he was working at the time. He was put on- then put on medication by the psychiatrist and was on this medication for about six months. And at that point he lost his job at Boeing because of his disability. He was hearing voices and seeing things and responding to internal stimuli that he was not able to function in that role anymore. And then he was placed on another medication and within six months he had his first involuntary hospitalization at Puget Sound and he- it took six sheriffs to get him into the ambulance and take him to the hospital he was so psychotic. And then he was stabilized on medication and seen at the Community Mental Health Center. And through the course of his illness, which he has refractory schizophrenia, he's been on all the atypical antipsychotics and he's tried on some of the typical antipsychotics, but currently he's on Clozaril because he has refractory schizophrenia. And so he never goes a day without symptoms. But he is able to live in the community. That's one benefit of these medications is that he can live with us in the community. He can't live independent because of his illness. And so I ask you as a mother of a person with schizophrenia, of a son, that you not prevent other people from having access to these medications. Every drug that we tried I was so ecstatic as a parent to be able to try this new medication, to be able to give him the opportunity to function in the community and have a normal life. And I just think that if you make barriers to treatment that you're going to really make it difficult for people that don't have the ability to advocate for their children. And I was really lucky. I think this disease has been a blessing and a curse. And the blessing is that I've been a nurse in psychiatry since 1984 and I know about the medications and I know how to advocate treatment. That there aren't people out there that have those same resources, especially people that are getting state funding. So I just ask you that you think about that when you restrict choice you restrict people's lives that are really suffering and have no choices. That's all I wanted to say. Thank you.

Dan Lessler: Thank you. And finally James Kelly. Just handed this for James Kelly. Have I missed anybody? Okay. Why don't you come up.

Andrew Davis: My name's Andrew Davis, I am a consumer from Bellingham. I'm representing myself. I've been diagnosed with a condition called paranoid delusional disorder. I've been on atypical antipsychotics for eight years. The first atypical antipsychotic that my doctor tried did not work for me. It did not alleviate the symptoms of my condition. The second atypical anti-psychotic that was tried worked very well for me. It was Risperdal. It worked so well it allowed me to go back to work. After being on Risperdal for six years it became apparent to my doctor that it was thinning my bones so it became necessary for me to switch to another atypical antipsychotic. I started taking Geodon. Geodon does not work as well as the Risperdal did. But since I was on Risperdal for six years I gained the insight

necessary for me to function on Geodon. I attribute the fact that I am employed today and paying taxes due to the fact that my doctor has had a wide variety of atypical antipsychotics to choose from in treating my mental illness. Thank you.

Dan Lessler: Thank you. I think there was somebody else back here that wanted- please.

Nancy Grosskreuger: Hi. My name is Nancy Grosskreuger. As an RN and a consumer with bipolar disorder and ADD, I'm pretty close to this topic. I've been depressed profoundly and suicidal since I was ten. I've been on every antidepressant in the book. And if I forget what I'm saying in the middle of something, I have neurological damage from an antidepressant that actually worked. So I have three weeks of happiness that I remember with this drug, but I can't function. I can't work now because I don't have short-term memory and my brain's all scrambled. Anyway, I'm medication resistant, I've been on everything. There are only two drugs that I can say I can really feel working; Depakote helps with my rapid cycling, definitely, and Geodon, which I discovered helps with- I didn't have a name for it but I guess I was paranoid. I would leave work and I would think people were talking about what a bad job I had done and, oh, my gosh did I leave some trash on the floor. Something like that. And I knew darn well they weren't thinking that. But Geodon helps to limit that. So with those two working, and then being on other meds and antidepressants and so forth, and support of my self-care that I really have to struggle- I struggle with depression every day. I go to [unclear] for the bipolar support groups, and I'm facilitating there. And possibly extending to the hospital nearby. And then I'm a peer specialist according to DBSA. I took a course with them. And I'd rather have side effects from atypicals- I tried different atypicals and the only one that worked is the Geodon. But I'd rather deal with side effects than to hate myself all the time and want to be dead 'cause I have a son and I can't do it to him. He would have a 50% chance of killing himself if I killed myself. So we need to have as many meds as is possible to try and treat these things, or, you know, people are going to die. You know. Maybe that's not important. But we've got a nursing shortage and I can't work. So thank you for having us and thank you for letting me speak.

Dan Lessler: Is there, again, anybody that we might have missed? I want to make sure everybody has an opportunity. No. Okay. Well, thank you very much. And thank you all for your input.

Jeff Graham: Oh, Dan…

Dan Lessler: Yeah.

Jeff Graham: Can I make a couple comments?

Dan Lessler: Yeah.

Jeff Graham: This is Jeff Graham. We just wanted to say thank you to everybody who came to testify today. A couple things that came out in the testimony [unclear]…

Dan Lessler: There you go.

Jeff Graham: Seems to be a concern that we're just looking at typicals. That's not true. We're not going to limit anybody just to typicals and not cover atypicals. The state has never said that. We don't think the committee would do that. Just some things, too, the committee, I believe, we will be making a decision at the next meeting. And we wanted to say that it doesn't matter, regardless of what their decision is, anybody that's on a typical antipsychotic at the present time that's a protected class and you always will have refills. And I think there's a little refill description- I'm not sure if it was out there for stakeholders, that we have for antidepressants. The same happens for anybody who would be on an atypical antipsychotic. So those are some of the things that we do have in place for protections for people who presently are on medications. We're not trying to second guess what the decision will be next time, but at least we know those things are already in place. And also there's something, a program that if your physician writes Dispense As Written in this class, then you would receive that drug too. So those are the things we already have in protection. But certainly we're going to be discussing this more at the next meeting.

Dan Lessler: Thanks. I also wanted to comment as well that, as Jeff said, we're going to begin our discussion this afternoon, but we'll be carrying it over to the next meeting before we make any recommendation. I appreciate- I think the committee appreciates the stakeholder input. And we will have time, as well, next time for stakeholder input, but we ask that if- we'd like to reserve that time for people who have not already had a chance to speak. If you already have spoken but have something that is new to add, you know, distinctly new, then you would be welcome to speak. So I just wanted to let people know a little bit about the process and ask that people who have spoken please allow those- that time, which we're reserving at the next meeting to people who have not had a chance to speak yet. So I think what we'll do now is take about a 15 minute break and resume here for discussion about five of three. Does that sound- okay. So we're adjourned 'til then.

Dan Lessler: I think that- I think everybody from the committee who is here today is back. So according to our agenda, actually, the way this was laid out we had additional time at this point anticipating that there might be more stakeholder input and wanting to make sure that we allowed adequate time for that. But we have been able to get through the stakeholder comment. Today we don't intend to actually formulate any kind of recommendation. And that will be- actually what we do when we start off in our- with our next meeting in June. I do think it would be helpful if we took just a brief amount of time here to maybe have members of the committee just engage a little bit of discussion, if only just to react and get some thoughts out about what we've heard today, both from the people at OHSU and from Dr. Farmer and from the stakeholders. That will be- that sort of discussion will be transcribed. And what I've asked is that it be sent back to us, actually along with- actually we're thinking the full transcript maybe about a week, before we're scheduled to meet in June. And I would ask, and I think it would be very helpful if people could just peruse that when it comes back because it will sort of jog people's memories as to where we were at, sort of some of the issues that were getting raised and so forth.

And it will help inform and make our discussion that much more efficient when we get started in June.

My understanding is, Dr. Farmer, you will be able to come back in June and we really welcome that you'll be there with us at that time. So, as I say, at this point I think maybe just if we could begin with P&T members engaged in just a little preliminary discussion, observations, reactions and so forth to what we've heard so far. And also, just to remind people, we have- Dr. Farmer is here if you want to address specific questions and engage her expertise.

Jeff Graham: This is Jeff Graham. I want to remind people to be sure to identify people to identify themselves and use the microphone because that's how we take the transcriptions. Just because we don't have a big crowd out here now, the main thing is to make sure we're getting all of this on the transcription.

Dan Lessler: So I would ask what do people make of it all?

Angelo Ballasiotes: Angelo Ballasiotes. I'd like to make a comment, and I think I see a real dilemma in I think this picture is a lot larger than we're able to see right now. And I'll give you some of my thoughts on this. Really a lot of pressure- I do work in a community health center, mental health center, in Yakima. And we get a lot of pressure to keep people out of a hospital. That's Eastern State Hospital and Western State Hospital. And you don't- it's kind of hard to tell you how we get pressured to get these people back in the community because that's where the drive is, that's what we want as a society. We want our mentally ill back in the community and functioning. So a lot of times we have to use a lot of different tools to do that. And it's really a community based effort with jobs, with case managers, with places for mentally ill people to go, things of this nature. So it's kind of a community within the community. I guess the point I'm trying to make here is to have a lot of you understand is it's bigger than just medications. But medication's a very important part of it. And also the jail situation. I do work every week in the jail and I see a lot of our patients in the jail that we cycle through. I see them on the outside and I see them on the inside. My specialty is co-[unclear] disorders, so I treat the mentally ill and also the substance abusers in that combination. So they're in and out of services all the time, on the medications, off their medications. It's an effort. And it's a little different, I think, than maybe the picture that's been painted here. I guess that's the comment that I want to make.

Dan Lessler: Thanks. Patti?

Patti Varley: This is Patti Varley and I just jotted down some things that I- comments basically based on what we've heard today and my thoughts. The first thing I wrote was none of them are perfect. And that, you know, I guess a plea I'd put out there is, you know, my hope sort of like the gentleman who testified is wouldn't it be nice if he could go off the Stelazine because all these other ones that are promising the world would work better. And I guess it's a plea to say, all that I hear, all that I see, all that I see in my practice as well as in this room makes me just think we need to look beyond what the list is now to something even better because I'm not quite that ecstatic about what we have. I think- the other thing that struck me is

regardless of which med you look at the compliance in this class is horrible. It's horrible because these are what I refer to in my own terminology, dirty drugs. Dirty drugs mean they come with a lot of side effects. And, you know, I'm a little hesitant that some of the newer ones are yet to be story told. And what I mean by that is I think a lot of- one of the legislatures said something about the data not being that great. And I think part of our problem, and it's no one's fault, is that the way this data comes out is very short term and that what we find in real life later are the side effects for real people. That the studies are done with sort of people that are selected, very narrow. They're not the real people all of us are seeing day in and day out, or the people who were testifying in this room necessarily. And so I'm hesitant to judge the older atypicals against some of the newer ones because I don't think fairly we have the data on the newer ones that we have on the older ones about long term good or bad and that makes it tough for me in regard to classifying one as better than the other.

I think we talked about, and I feel like this has been true from the beginning, which is dosage issues, that it's hard to look at studies that use dosages that now we clinically find are not the right dosage. They were either too high or too low and now in real life the dosage we use isn't the dosage that was used in some of the data or studies we're reviewing. And, you know, without it being said- it's been said and it needs to be said again, nobody's talking here about the newer are better than the older, the atypicals are better than typicals, they're just far from perfect. And nobody's talking about going back to the typicals. I just want to be clear on that.

But I think the other part that I thought about is this is a very tough to treat population. They are- it's very challenging. And we heard that in our stories and I think those of us who work clinically find that to be true as well. And that this is an incredibly severe illness. And incredibly chronic illness and incredibly costly disorders that we're talking about in regard to schizophrenia or bipolar disorder. And costly in a number of ways; financially, but also emotionally and socially. And I think the other issue had to do with we talked so much about looking at the evidence based medicine with side effects and risks and all that, but as you heard in the testimony and as I see to be true clinically, some people will choose a side effect for control of this illness. And they would rather live with that side effect than try to go off of something that gives them some control of an illness. And I think we have to be cautious as we look at it out here as to whether that side effect is or is not something an individual with this disease wants to tolerate. And so that made me a little concerned as well. I would say, you know, I'm partially doing this, I should clarify, because I will not, unfortunately, be here in June because I will be out of town.

And I just want to state for the record that the other thing is that I think as you look at the list the route needs to be considered as far as having agents that are able to be delivered through different routes. Having to do with, again I work in a pediatric population, but you're also talking about people who at times are severely ill or metabolism wise need different ways of the medicine to be distributed.

And last I'm looking over to this side of the room saying I'm very much looking forward to the outcome of Mental Health Committee's review of this class because I applaud you in taking on that challenge of what you're about to endeavor on. Thank you so much.

Dan Lessler: Thank you, Patti. All helpful comments. We can equip you with a satellite phone. Jeff has said that we can reach you up in Alaska. Other reactions, comments or observations just about the class or any- what we've heard today in terms of beginning the process of thinking through a recommendation? Carol?

Carol Cordy: This is Carol Cordy. A couple of things. I can't remember who it was mentioned an education piece of educating prescribers. I don't know if that's going to come out of your committee or where, but I think this is one of the classes that as we were going through I was thinking of a scale of which drug would you prescribed, you know, you put a penny in this one and put a penny in this one. And it just was very confusing as to which of these in these studies would be better for whom. And what I'd like to see come out of this is some kind of a flow sheet. We all love protocols and flow sheets that would give us some clue. Because I think these medications are medications that are being prescribed in primary care, not just in psychiatry. So that at least we'll be doing a better job of picking a medication that will be right for a particular patient. So what I'd like to see is some of that education piece come out of it.

And the question I had of Dr. Farmer and anyone else who wants to comment is, Was there anything in this presentation that you heard today that would change how you prescribe- or how you are prescribing medications right now?

Sharon Farmer: Are you talking about the presentation…

Carol Cordy: From this morning.

Sharon Farmer: from the stakeholders?

Carol Cordy: No, no. I was talking about…

Sharon Farmer: You were talking about OSHU.

Carol Cordy: Yeah.

Sharon Farmer: I think it's highlighted the significance and- or the lack of significance in the research on some of the side effects. So I I have found that useful and it's helped me select medications for people.

Carol Cordy: And to follow upon that, those- I think those would also be part of the education piece if there's something in all this information that's confusing when you try and get your head around it.

Sharon Farmer: We're actually working on that right now. We're trying to make some tables that select the significant differences, both in terms of positive results, and in terms of

side effects. And I'm hoping that we'll make those available to prescribers. I don't think it's going to be a flow sheet. And I don't think that that would really be possible. I think there's too many individual aspects about the medicines and each patient that really have to be matched. And so a flow sheet would probably not work. And I will point out to you the Texas Medication algorithm Project. They've been working on a flow sheet type algorithm for schizophrenia and I think they now are probably on their third edition of that. And it does not specify which atypical you would start with. And I think that that's the reason why.

Dan Lessler: Where is that?

Sharon Farmer: Where is it? It's the Texas Medication Algorithm Project.

Dan Lessler: Right. We saw that here at some point. Thanks. Jeff, I was wondering if you want to just-had any general comment. But also I was interested, you know, Carol brings up the good point, I'm just curious about the relative prescribing by psychiatrists versus generalists of these medicines, at least with respect to medicate.

Jeff Thompson: Well, I'll just run through the numbers. This is Jeff Thompson. We have approximately 28,000 clients that are on atypical antipsychotics. That's 2005 data. It's about a $64 million spend. We have all age ranges from less than 1 up to 101 on this. And I just ran the numbers. We have I think 65 less than five year olds on antipsychotics. And so I think one of the things with the group that we'll be looking at is looking at safety issues first. I mean, looking at age issues, looking at combinations. Looking at dosing limits when we- I think there's about 9% of our population exceed the FDA dosing. And about 4% of our under 18 year olds exceed FDA dosing. Looking at this we find that about 2/3 of our clients have touched the mental health division and the other 1/3 have not. When you look at some data coming out of Texas you'll find that about 80% of these are prescribed by psychiatrists and 20% by the pediatricians or primary care physicians. So it's not exclusive to just the psychiatric community. So out of that 2/3 of mental health the third in somebody else. It certainly is affecting our foster care children in what we do, so we've been meeting with the children's organization. It's certainly going to affect ADSA with our DD clients and age clients both in residential and nursing homes. We've had meetings with them. And then we're also having extensive meetings with the mental health division, not only just with the bureaucrats, but also we're going into the hospital and having some discussions with Eastern and Western State and talking about do we have competing or can we have similar goals, inpatient and outpatient.

So I think with the Mental Health Work Group we're going to be looking at all those things and try to just- a simple communication, what's happening out there, what is sort of the state of the state looking at these. What are some recommendations. Probably learn from our ADHD experience. Perhaps maybe some second opinion process when we're looking at some rather strange combinations or excessive dosing. And so far we're learning, I think, a lot of what's going on. Might ask Sharon or Dick or Mark about what they're seeing when we bring forward with some of this data. Hopefully that helps.

Bob Bray: Bob Bray. Jeff, I'm wondering, my seat of the pants guess in Spokane is the vast majority of the patients that are on Clozaril are probably medicated and are probably prescribed by the Community Mental Health Center there, which is Spokane Mental Health. And we haven't had any advocates for Clozaril today, which I'm just now realizing might be kind of unexpected, but I'm guessing whatever comes out of here- how does that- how does what we do here affect things like that where obviously that's a very important treatment that has been determined by psychiatrists? And my guess is a lot of these folks are multiple treatment failures and so on. So, is Clozaril going- and it's not prescribed by anyone outside of these restricted systems. So is Clozaril going to be handled separately than the other drugs? Or have we- or do you know?

Jeff Thompson: We really haven't had a discussion about that. I think, you know, one thing is I just want to start the discussion about let's look at where the prescribing patterns are and where we see safety concerns. Let's start there. That's primarily what I'm concerned with.

Sharon Farmer: I'll just point out that Clozaril is available in a generic form. And I think that's probably why there was no pharmaceutical company here advocating for it.

Dan Lessler: Mark, did you have a comment?

Male: [unclear- off mic]

Male: I appreciate that and I might have misspoken. That's what I'm talking about, too. It's not the community healthy options part but the community mental health centers and the MAA fee for service. That is what I was speaking about.

Male: [unclear- off mic]

Dan Lessler: Did you have a quick comment…

Female: Can I- oh.

Male: [unclear- off mic]

Dan Lessler: Yeah, go ahead.

Nicole Nguyen: This is Nicole Nguyen. I just wanted to add about the Healthy Option clients that do self- refer to community mental health, their mental health drugs are actually carved out of Healthy Options and come [unclear]. I just wanted to add on to what Dr. Avery said.

Dan Lessler: Jeff?

Jeff Thompson: And I- just my comment. When I'm talking about safety we're looking at both under use, misuse, over use, poly pharmacy, poly prescribing, because you only know what happens in your clinic. And what we found out was every single drug- there may be two, three or four prescribers for one client. So the one thing I'm

hoping we'll get to is giving you data so you know what happens outside that 20, 15 minute interview. And we're learning from the narcotic review, too, that we can give you not only their inpatient history, we can give you their ER history, we can give you who's prescribing what to whom when. And it's an eye opener to physicians. So it goes beyond just the typical age, dose combination discussions.

Dan Lessler: Jeff, I'm wondering from a policy standpoint whether in other states where a decision, for example, has been made to limit atypicals if people have done sort of a naturalistic outcome study and what that's show. I'm reminded of the famous, sort of naturalistic study that was done in New Hampshire when the legislature there restricted the number of medications to five and saw a terrific increase in the number of patients going into skilled nursing facilities as a result. So I'm just curious a policy level whether there's anything that informs that.

Jeff Thompson: We've looked at- we've benchmarked 18 states and where they are on the Preferred Drug List as it relates to antipsychotics. And there are some Preferred Drug List selections that states are making, I believe, that there are about 9 states that have done a Preferred Drug List. There are about five states that have said pretty much sort of open access. And then there's a combination of dose, prescriber type, you know, maximum dosing, prior authorizations for certain ones. But when you look at these all of these have been very new. So there is no outcome data on what's happening. And I think we're going to try and make a commitment to looking at our outcome. Right now I've talked to Sharon and we're looking at what is our churn in patients that are going from aging and disability services into Eastern and Western state and then back out again. How many people actually do that churn? Once a year, twice a year, three times a year. So we're looking at that data. 'Cause that's some of the safety data I'm concerned about.

Dan Lessler: Thanks. Other comments here? Ken, do you have a…

Ken Wiscomb: Ken Wiscomb. My only thought was, you know, this is very complicated. I think it's going to be a very difficult decision. In the past we've had to look at efficacy and outcome first. We've had the luxury, I guess, of looking at efficacy and outcome first and safety and cost as secondary issues. I think, although we may not specifically address them, in this instance we're going to have to consider off label uses. We're going to have to consider different combinations of things that are a reality out there, that we may not necessarily address specifically but we anticipate they're going to happen. It's going to make it very difficult.

Dan Lessler: Other thoughts. Jeff, I was wondering if you want to put it all together here, wrap it up, summarize the- you're very good at that.

Jeff Thompson: I might mention- I don't know if the committee- again, this is Jeff Thompson. There is another study out there that you should take a look at. We did commission the Rand Corporation to look at off label use. So there are eight diagnoses that Rand has done a tandem to OSHU that we'll provide you with. I think we can give 'em hard copies at this point.

Dan Lessler: Actually, that brings up another questions, which is probably more of a procedural point that I would address to Jeff, perhaps. And that has to do with the second part of the CATIE study, which I'm not sure when that's going to be released but my understanding is it's soon. And whether or not if it becomes available in the interim that's something we can look at. Obviously whatever sort of medicines you're talking about it's always sort of dynamic in terms of the information base that you're working with. And, you know, at some point in time you've got to make a decision. So I'm wondering if you might comment on that, Jeff.

Jeff Graham: First I can say- this is Jeff Graham, the next update for this class is just beginning, because this one was just finished. It will be started immediately and so we would expect the CATIE II to be published by that time and be included. Or maybe it has been published. But I- has it, Jeff?

Jeff Thompson: I [unclear] heard that it just has come out in publication.

Jeff Graham: So it would be included. Would we bring that forward for our considerations for- at the next meeting?

Dan Lessler: June, right.

Jeff Graham: In June? I'm not saying we can't do that. We've generally not done that. It would be nice to have somebody look at it very critically before we present that. I'm not certain- everybody says we have to wait for this study, this study. What we're finding is that it doesn't seem to add a whole lot.

Dan Lessler: I agree. And we could end up waiting for Goudeau here, right. So I- but I just thought as a matter in this case with that particular study close to publication just to have some clarification as to whether or not we would look at it or…

Sharon Farmer: They have put out two publications. I just got them on my desk yesterday and so I quickly copied the abstracts. And I don't think that it's going to actually contribute a whole lot to this committee. It did- I think the main finding was that people who got- who dropped out of Phase I because they weren't getting good results, not because they dropped out because they had side effects. But they weren't getting good results. They had the option of being randomized into the Clozaril arm and Clozaril seemed to do really well. And the reason I'm saying I don't think that's going to make much difference for this committee is that I'm assuming that Clozaril is going to be on the Preferred Drug List because it is generic, I think there's some evidence that it has some special value. And then I don't see a lot of people running to it, though, because it also has special problems. So I don't think CATIE's going to have more to add than that.

Dan Lessler: Thank you. That's very helpful. And for the transcriptionist and the record it's going to say that was Dr. Farmer speaking.

Patti Varley: And this is Patti Varley and I'll just ask if it's possible and that is I don't know if it is, and if it would serve the committee's purpose to ask, or again to just look at it

for us, and briefly summarize it for that June meeting so that you've technically gone through the same place for review. I'm just asking.

Dan Lessler: All right. Can we do that?

Male: [unclear- off mic]

Dan Lessler: Okay. Just sort of a limited commentary, although I think Dr. Farmer probably has just provided us with that very nicely. Other comments here or thoughts? Bob.

Bob Bray: Bob Bray. It does seem kind of funny that we would think about making a decision before the Mental Health Task Force is finished what they're doing in evaluating this. So was there a point at which it's anticipated that will be ready for us to look at? Or is that unknown still? The conclusion of the Mental Health Task Force on the atypical.

Jeff Thompson: I think we'll have- I mean, this Friday we're meeting again, so we're going to have our tables and we'll- can get those, I think, filled out in a couple weeks. And I've sort of been doing a little background work. Again, this is Jeff Thompson. And I think the PowerPoint that they actually put in there is incredibly useful and sums up a lot of this. I mean, this is without Rand. I mean, this is the whole thing. So I think we can at least get to harm and benefit pretty quickly. And then the rest of the work is really looking at what does the evidence say for off label use. And again, I don't think we're in the business of doing algorithms here. I think it's mostly education about, you know, what is the harm benefit. And I think now that they've actually put some intention to treat or number needed to treat, number needed to harm, you can actually do some comparisons now. I think they did a very nice job in this review here.

Female: Can I just add one more comment? And I'm just speaking for myself here and not so much the committee. But I'm anticipating- I know that this group to some degree is hoping to make decisions that make sense clinically but also economically. And our committee is just starting to look at some of the data. And I'm thinking that we will find a fair amount of unnecessary use of atypicals. The classic example is Seroquel being used to help people sleep and for anxiety. I think that's probably overkill for those symptoms. And then I think also another issue that we're going to look at really closely is people who are on multiple antipsychotics. And I'm hoping, although I hope we do this very gradually and gingerly, that we'll be able to have some of those people who might have been started on [unclear] medicine in an acute setting but not really need it long term be able to go off their medication. So I'm hoping that we'll be able to make some recommendations that will help safety, but also help some of the economic issues in a way that really will not contribute to harm.

Dan Lessler: Thank you. Well, it's about 3:30 and I think we've had a very good discussion and that will be part of the record that we can all review will help us when we reconvene in a few months to actually consider and put forth a recommendation. So I think we'll stop here and adjourn. I thank everyone for coming and I

especially thank Dr. Farmer for your assistance and I'm glad you're going to be able to join us next time as well. So, thank you. We're adjourned.